0/1-Hour Triage Algorithm for Myocardial Infarction in Patients With Renal Dysfunction

Twerenbold, Raphael ; Badertscher, Patrick ; Boeddinghaus, Jasper ; Nestelberger, Thomas ; Wildi, Karin ; Puelacher, Christian ; Sabti, Zaid ; Rubini Gimenez, Maria ; Tschirky, Sandra ; du Fay de Lavallaz, Jeanne ; Kozhuharov, Nikola ; Sazgary, Lorraine ; Mueller, Deborah ; Breidthardt, Tobias ; Strebel, Ivo ; Flores Widmer, Dayana ; Shrestha, Samyut ; Miró, Òscar ; Martín-Sánchez, F Javier ; Morawiec, Beata ; Parenica, Jiri ; Geigy, Nicolas ; Keller, Dagmar I ; Rentsch, Katharina ; von Eckardstein, Arnold ; Osswald, Stefan ; Reichlin, Tobias ; Mueller, Christian

Abstract: BACKGROUND The European Society of Cardiology recommends a 0/1-hour algorithm for rapid rule-out and rule-in of non-ST-segment elevation myocardial infarction using high-sensitivity cardiac troponin (hs-cTn) concentrations irrespective of renal function. Because patients with renal dysfunction (RD) frequently present with increased hs-cTn concentrations even in the absence of non-ST-segment elevation myocardial infarction, concern has been raised regarding the performance of the 0/1-hour algorithm in RD. METHODS In a prospective multicenter diagnostic study enrolling unselected patients presenting with suspected non-ST-segment elevation myocardial infarction to the emergency department, we assessed the diagnostic performance of the European Society of Cardiology 0/1-hour algorithm using hs-cTnT and hs-cTnI in patients with RD, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m2, and compared it to patients with normal renal function. The final diagnosis was centrally adjudicated by 2 independent cardiologists using all available information, including cardiac imaging. Safety was quantified as sensitivity in the rule-out zone, accuracy as the specificity in the rule-in zone, and efficacy as the proportion of the overall cohort assigned to either rule-out or rule-in based on the 0- and 1-hour sample. RESULTS Among 3254 patients, RD was present in 487 patients (15%). The prevalence of non-ST-segment elevation myocardial infarction was substantially higher in patients with RD compared with patients with normal renal function (31% versus 13%, P<0.001). Using hs-cTnT, patients with RD had comparable sensitivity of rule-out (100.0% [95% confidence interval CI, 97.6-100.0] versus 99.2% [95% CI, 97.6-99.8]; P=0.559), lower specificity of rule-in (88.7% [95% CI, 84.8-91.9] versus 96.5% [95% CI, 95.7-97.2]; P<0.001), and lower overall efficacy (51% versus 81%, P<0.001), mainly driven by a much lower percentage of patients eligible for rule-out (18% versus 68%, P<0.001) compared with patients with normal renal function. Using hs-cTnI, patients with RD had comparable sensitivity of rule-out (98.6% [95% CI, 95.0-99.8] versus 98.5% [95% CI, 96.5-99.5]; P=1.0), lower specificity of rule-in (84.4% [95% CI, 79.9-88.3] versus 91.7% [95% CI, 90.5-92.9]; P<0.001), and lower overall efficacy (54% versus 76%, P<0.001; proportion ruled out, 18% versus 58%, P<0.001) compared with patients with normal renal function. CONCLUSIONS In patients with RD, the safety of the European Society of Cardiology 0/1-hour algorithm is high, but specificity of rule-in and overall efficacy are decreased. Modifications of the rule-in and rule-out thresholds did not improve the safety or overall efficacy of the 0/1-hour algorithm. CLINICAL TRIAL REGISTRATION URL: https://www.clinicaltrials.gov. Unique identifier: NCT00470587.

DOI: https://doi.org/10.1161/CIRCULATIONAHA.117.028901

Originally published at:
Twerenbold, Raphael; Badertscher, Patrick; Boeddinghaus, Jasper; Nestelberger, Thomas; Wildi, Karin; Puelacher, Christian; Sabti, Zaid; Rubini Gimenez, Maria; Tschirky, Sandra; du Fay de Lavallaz, Jeanne; Kozhuharov, Nikola; Sazgary, Lorraine; Mueller, Deborah; Breidthardt, Tobias; Strebel, Ivo; Flores Widmer, Dayana; Shrestha, Samyut; Miró, Òscar; Martín-Sánchez, F Javier; Morawiec, Beata; Parenica, Jiri; Geigy, Nicolas; Keller, Dagmar I; Rentsch, Katharina; von Eckardstein, Arnold; Osswald, Stefan; Reichlin, Tobias; Mueller, Christian (2018). 0/1-Hour Triage Algorithm for Myocardial Infarction in Patients With Renal Dysfunction. Circulation, 137(5):436-451.
DOI: https://doi.org/10.1161/CIRCULATIONAHA.117.028901

0/1-Hour Triage Algorithm for Myocardial Infarction in Patients With Renal Dysfunction

Editorial, see p 452

Raphael Twerenbold, MD et al

BACKGROUND: The European Society of Cardiology recommends a 0/1-hour algorithm for rapid rule-out and rule-in of non–ST-segment elevation myocardial infarction using high-sensitivity cardiac troponin (hs-cTn) concentrations irrespective of renal function. Because patients with renal dysfunction (RD) frequently present with increased hs-cTn concentrations even in the absence of non–ST-segment elevation myocardial infarction, concern has been raised regarding the performance of the 0/1-hour algorithm in RD.

METHODS: In a prospective multicenter diagnostic study enrolling unselected patients presenting with suspected non–ST-segment elevation myocardial infarction to the emergency department, we assessed the diagnostic performance of the European Society of Cardiology 0/1-hour algorithm using hs-cTnT and hs-cTnI in patients with RD, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2, and compared it to patients with normal renal function. The final diagnosis was centrally adjudicated by 2 independent cardiologists using all available information, including cardiac imaging. Safety was quantified as sensitivity in the rule-out zone, accuracy as the specificity in the rule-in zone, and efficacy as the proportion of the overall cohort assigned to either rule-out or rule-in based on the 0- and 1-hour sample.

RESULTS: Among 3254 patients, RD was present in 487 patients (15%). The prevalence of non–ST-segment elevation myocardial infarction was substantially higher in patients with RD compared with patients with normal renal function (31% versus 13%, *P*<0.001). Using hs-cTnT, patients with RD had comparable sensitivity of rule-out (100.0% [95% confidence interval {CI}, 97.6–100.0] versus 99.2% [95% CI, 97.6–99.8]; *P*=0.559), lower specificity of rule-in (88.7% [95% CI, 84.8–91.9] versus 96.5% [95% CI, 95.7–97.2]; *P*<0.001), and lower overall efficacy (51% versus 81%, *P*<0.001), mainly driven by a much lower percentage of patients eligible for rule-out (18% versus 68%, *P*<0.001) compared with patients with normal renal function. Using hs-cTnI, patients with RD had comparable sensitivity of rule-out (98.6% [95% CI, 95.0–99.8] versus 98.5% [95% CI, 96.5–99.5]; *P*=1.0), lower specificity of rule-in (84.4% [95% CI, 79.9–88.3] versus 91.7% [95% CI, 90.5–92.9]; *P*<0.001), and lower overall efficacy (54% versus 76%, *P*<0.001; proportion ruled out, 18% versus 58%, *P*<0.001) compared with patients with normal renal function.

CONCLUSIONS: In patients with RD, the safety of the European Society of Cardiology 0/1-hour algorithm is high, but specificity of rule-in and overall efficacy are decreased. Modifications of the rule-in and rule-out thresholds did not improve the safety or overall efficacy of the 0/1-hour algorithm.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00470587.

The full author list is available on page 448.

Correspondence to: Christian Mueller, MD, Department of Cardiology, Cardiovascular Research Institute Basel, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland. E-mail christian.mueller@usb.ch

Sources of Funding, see page 449

Key Words: 0/1-hour algorithm ■ chronic kidney disease ■ diagnosis of acute myocardial infarction ■ high-sensitivity cardiac troponin ■ renal dysfunction

Clinical Perspective

What Is New?

- The 0/1-hour algorithms using high-sensitivity cardiac troponin for rapid triage of patients with suspected myocardial infarction are increasingly used in clinical practice worldwide.
- Although their high safety and efficacy could be shown in the general, mixed setting of emergency departments, their utility in patients with renal dysfunction, presenting with elevated high-sensitivity cardiac troponin levels often in the absence of acute myocardial ischemia, has been questioned.
- For the first time, we demonstrated the excellent safety of the 0/1-hour algorithms using high-sensitivity cardiac troponin T and high-sensitivity cardiac troponin I also in patients with renal dysfunction, whereas overall efficacy and rule-in specificity were reduced compared with patients with normal renal function.

What Are the Clinical Implications?

- The investigated 0/1-hour algorithms for rapid triage of patients with suspected myocardial infarction provide high safety irrespective of renal function and do not seem to require adjustment for renal function.
- However, the proportion of patients eligible for rule-out is reduced in patients with renal dysfunction compared with patients with normal renal function (≈ factor 3) because of the substantially higher prevalence of myocardial infarction in patients with renal dysfunction (≈ factor 3).

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide. Its rapid and accurate diagnosis is critical for the initiation of effective evidence-based medical management and treatment.[1–3] In addition, its rapid and reliable rule-out has the potential to reduce the time spent in the emergency department (ED), accelerate the identification and treatment of the actual cause of chest pain, reduce patients' anxiety, and avoid substantial costs for the healthcare system.[4,5]

For several reasons, patients with renal dysfunction merit particular attention.[6,7] First, the incidence of AMI is increased in this vulnerable subgroup.[8–10] Second, atypical clinical presentation of AMI may be more frequent.[11,12] Third, left ventricular hypertrophy is common and often results in ECG changes that may mimic or obscure AMI. Fourth, patients with renal dysfunction are more prone to adverse events related to cardiovascular medication (eg, anticoagulation) as well as cardiovascular procedures, including coronary angiography and coronary intervention.[1,2] Fifth, levels of cardiac troponin (cTn) are frequently chronically elevated even in the absence of AMI.[6,10,13] Recently, sensitive and high-sensitivity cardiac troponin assays (hs-cTn) were demonstrated to be accurate tools in diagnosing AMI in patients with renal dysfunction, particularly when adjusted slightly higher cutoff levels are used for clinical decision making.[10]

The latest guidelines of the European Society of Cardiology (ESC) for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation recommend the use of a 0/1-hour algorithm to rapidly rule out and rule in non–ST-segment elevation myocardial infarction (NSTEMI) based on hs-cTn concentrations at presentation and their absolute 1-hour changes.[1] Assay-specific cutoff values are recommended for uniform application irrespective of renal function. High safety and efficacy of the 0/1-hour algorithm were demonstrated in unselected patients, of which the vast majority had normal renal function. It is unknown whether these results also apply to patients with renal dysfunction (RD).[1,14–19] Because patients with RD frequently present with increased hs-cTn concentrations even in the absence of NSTEMI, concern has been raised regarding the performance of the 0/1-hour algorithm in RD.[10]

We therefore aimed to assess the diagnostic performance of the ESC 0/1-hour algorithm in patients with RD in a large prospective multicenter diagnostic study.

METHODS

Study Design and Population

APACE (Advantageous Predictors of Acute Coronary Syndrome Evaluation) is an ongoing prospective international multicenter diagnostic study with 12 centers in 5 European countries aiming to advance the early diagnosis of AMI (ClinicalTrials.gov. Unique identifier: NCT00470587).[10,15–17,20,21] Adult patients presenting to the ED with symptoms suggestive of AMI (eg, acute chest discomfort and angina pectoris) with an onset or peak within the last 12 hours were recruited. Enrollment was independent of renal function, whereas patients with terminal kidney failure on chronic dialysis were excluded. For this analysis, patients with ST-segment elevation myocardial infarction, patients with missing creatinine measurement, patients in whom the final diagnosis remained unclear even after central adjudication and ≥1 elevated hs-cTnT concentration possibly indicating AMI, as well as patients with no available hs-cTnT (for dataset A) or hs-cTnI (for dataset B) concentrations determined on presentation to the ED and after 1 hour were also excluded. Dataset B represents a subset of dataset A. The most common reasons for misvsing samples after 1 hour were early transfer to the catheter laboratory or coronary care unit and diagnostic procedures around the 1-hour window that precluded blood draw at 1 hour.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients. The authors designed the study, gathered

and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish. The STARD Checklist (Standards for Reporting of Diagnostic Accuracy Studies) can be found in Table I in the online-only Data Supplement.[22] The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Routine Clinical Assessment

Patients underwent clinical assessment that included medical history, physical examination, and standard blood tests including serial measurements of local hs-cTn, 12-lead ECG, chest radiography, continuous ECG rhythm monitoring, and pulse oximetry. Management of patients was left to the discretion of the attending physician.

Adjudicated Final Diagnosis

Adjudication of the final diagnosis was performed by 2 independent cardiologists at the core laboratory (University Hospital Basel) applying the universal definition of AMI using 2 datasets: (1) all available medical records obtained during clinical care, including history, physical examination, results of laboratory testing including serial clinical hs-cTn levels (according to onsite used hs-cTn assay obtained from clinical blood samples), radiological testing, ECG, echocardiography, cardiac exercise test, lesion severity, and morphology in coronary angiography pertaining to the patient from the time of ED presentation to 90-day follow-up; and (2) study-specific assessments, including detailed chest pain characteristics using 34 predefined criteria, serial hs-cTnT blood concentrations obtained from study samples, and clinical follow-up by telephone or mail. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

AMI was defined and hs-cTn interpreted as recommended in the current guidelines.[1–3,14] In brief, myocardial infarction was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by ≥1 cTn value >99th percentile together with a significant rising or falling. The criteria used to define a rise or fall in conventional cTn and hs-cTnT are described in detail in the Methods section in the online-only Data Supplement. All other patients were classified in the categories of unstable angina, noncardiac chest pain, cardiac but noncoronary disease (eg, tachyarrhythmias, perimyocarditis), and symptoms of unknown origin with normal levels of hs-cTnT.

Assessment of Renal Function

Renal function was quantified by estimating glomerular filtration rate (eGFR) with the use of the chronic kidney disease epidemiology collaboration formula based on plasma creatinine level obtained at presentation to the ED, age, sex, and ethnicity.[23] For this analysis, RD was defined as an eGFR of <60 mL/min/1.73 m.^{2} Creatinine measurements were performed on a Roche Modular P1 analyzer with the enzymatic creatinine-peroxidase-antiperoxidase PAP method for quantification (Roche Diagnostics). Serum creatinine can be converted from micromoles per liter to milligrams per deciliter by dividing by 88.4. Preexisting kidney dysfunction was documented based on previous hospital records and detailed patient history at the time of ED presentation.

Investigational hs-cTn Measurements

Blood samples for determination of hs-cTnT and hs-cTnI were collected into tubes containing potassium EDTA (as an anticoagulant) or serum gel (as a clot activator) at presentation to the ED and serially thereafter. Serial sampling was discontinued when a patient was discharged or transferred to the catheter laboratory for treatment. After centrifugation, samples were either analyzed directly or frozen at −80°C until they were assayed in a blinded fashion in a dedicated core laboratory.

According to the manufacturer, the hs-cTnT assay (Elecsys 2010 high-sensitivity troponin T, Roche Diagnostics) has a 99th percentile concentration of 14 ng/L with a corresponding coefficient of variation of 10% at 13 ng/L.[24] Limit of blank and limit of detection have been determined to be 3 ng/L and 5 ng/L. None of the hs-cTnT measurements in this analysis were affected by the 2010 to 2012 calibration shift.[25–28]

The hs-cTnI assay (ARCHITECT High Sensitive *STAT* Troponin I, Abbott Laboratories) has a 99th percentile concentration of 26.2 ng/L with a corresponding coefficient of variation of <5% and a limit of detection of 1.9 ng/L.[29–31]

Distributions of the latest study blood samples according to time since ED presentation and time since chest pain onset are listed in Tables II and III in the online-only Data Supplement.

ESC hs-cTn 0/1-Hour Algorithm

Recent studies have highlighted fundamental differences in mortality risk, pathophysiology, and benefit from early coronary angiography and intense dual-antiplatelet therapy between patients with NSTEMI and patients with true unstable angina (not including patients with small NSTEMIs missed by conventional cTn assays).[1,32] Accordingly, the immediate task in the ED is to detect NSTEMI. Thus, the ESC 0/1-hour algorithm was designed to detect NSTEMI. The diagnosis of unstable angina is based on clinical assessment, ECG, and rule-out of NSTEMI in the ED, as well as cardiac imaging performed either in-hospital or on an outpatient basis.[1,32]

The ESC hs-cTn 0/1-hour algorithm, which should always be used in conjunction with all clinical information available, including the ECG, triages patients presenting with suspected NSTEMI toward rule-out, observe, and rule-in based on assay-specific levels of hs-cTn obtained at presentation and after 1 hour (Figure I in the online-only Data Supplement).[1] The assay-specific cutoff levels were derived in diagnostic studies enrolling unselected patients with mostly normal renal function.[1,14–19]

Main Outcome Measures

The coprimary outcome measures were safety of rule-out, accuracy of rule-in, and overall efficacy of the ESC 0/1-hour algorithm in patients with RD. Safety was quantified as sensitivity for NSTEMI in the rule-out group, accuracy as specificity for NSTEMI in the rule-in group, and overall efficacy as the proportion of patients triaged to either rule-out or rule-in

based on the 0- and 1-hour sample. Because prevalence of NSTEMI differs between patients with RD and patients with normal renal function,[10] the negative predictive value (NPV) for NSTEMI in the rule-out group and the positive predictive value (PPV) in the rule-in group, which both depend on prevalence, were considered as secondary outcome measures. Additional secondary outcome measures included the proportion of patients assigned directly to rule-out or rule-in based on the single hs-cTn concentration measured at presentation.

Subgroup analyses assessing the diagnostic performance of the 0/1-hour algorithm were performed in early presenters (≤2 hours after chest pain onset), in patients with preexisting and new onset of RD, in women and men, and in the dataset after exclusion of patients who were part of the initial derivation cohort of the 1-hour algorithms.

To extend and corroborate the concept of the ESC 0/1-hour algorithm in patients with RD, diagnostic performance was further assessed using stepwise modified cutoff criteria optimized for patients with RD using hs-cTn concentrations at presentation or absolute changes within the first hour.

Follow-Up and Clinical End Points

Patients were contacted 3, 12, and 24 months after discharge by telephone calls or in written form. Information regarding death during follow-up was furthermore obtained from the patient's hospital notes, the family physician's records, and the national registry on mortality. The coprimary prognostic end points were overall survival after 30 days and 2 years. The secondary prognostic end point was major adverse cardiac events (MACEs), defined as the composite of all-cause mortality, AMI (including index event), cardiogenic shock, ventricular tachyarrhythmias, or higher degree atrioventricular block at 30 days.

Statistical Analysis

All data are expressed as medians (1st quartile, 3rd quartile) for continuous variables and for categorical variables as numbers and percentages. Continuous variables were compared with the Mann-Whitney U test, and categorical variables using the chi-square test or Fisher exact test as appropriate. Receiver operating characteristics curves were constructed to assess the discriminative performance throughout hs-cTn concentrations at presentation and their absolute changes in ≤1 hour to diagnose NSTEMI. The comparison of independent areas under the receiver operating characteristics curve was performed as recommended by Hanley and McNeil.[33]

We used the cross tables derived by the application of the official ESC assay-specific cutoff criteria for rule-out or rule-in to calculate diagnostic performance parameters and their 95% confidence intervals (CI).[34] To compare sensitivity, specificity, NPV, PPV, and efficacy, we used a chi-square or Fisher exact test for unpaired samples and the McNemar test or the method described by Moskowitz and Pepe[35] for paired samples, as appropriate. Correlations between renal function and concentrations/changes of hs-cTn were determined with the use of the Spearman rank correlation based on log-transformed hs-cTn values.

Overall survival and MACE-free survival during follow-up according to the classification provided by the respective 0/1-hour algorithm were plotted in Kaplan-Meier curves, and a log-rank test was used to assess differences in survival among groups.

Unless stated otherwise, results are reported based on dataset A. All hypothesis testing was 2-tailed, and *P* values of <0.05 were considered to indicate statistical significance without adjustments for multiple testing. All statistical analyses were performed with the use of IBM SPSS Statistics for Windows, version 23.0 (SPSS Inc), R statistical software version 3.4.1 (www.R-project.org, R Foundation for Statistical Computing), and MedCalc Statistical Software, version 17.8 (MedCalc Software bvba).

RESULTS

Patient Characteristics

From 4323 consecutively recruited patients, serial hs-cTnT measurements at presentation and after 1 hour were available in 3254 patients (dataset A, 100%) and serial hs-cTnI measurements in 2949 patients (dataset B) (Figure II in the online-only Data Supplement). Baseline characteristics are depicted in the Table 1 and Table IV in the online-only Data Supplement. Dataset B represented a subset of dataset A (overlap, 91%) (Table V in the online-only Data Supplement). Prevalence of RD was 15% (487/3254 in dataset A, 445/2949 in dataset B) with a median eGFR of 48 (37, 55) ml/min/1.73 m^2 as compared with 93 (81, 104) ml/min/1.73 m^2 in patients with normal renal function. Patients with RD differed from patients with normal renal function in multiple baseline characteristics, including higher prevalence of cardiovascular risk factors, previous myocardial infarction, and ECG abnormalities.

Adjudicated Final Diagnosis

NSTEMI was the adjudicated final diagnosis in 515 of 3254 (16%) patients. In patients with RD, prevalence of NSTEMI was 31% compared with 13% in patients with normal renal function (*P*<0.001). The prevalence of NSTEMI was significantly higher in those patients with RD who had preexisting kidney disease (37% versus 24%, *P*=0.002). Among all NSTEMIs, type 2 NSTEMI was more frequent in patients with RD compared with patients with normal renal function (22% versus 10%, *P*<0.001) (Table VI in the online-only Data Supplement), resulting in an overall type 2 NSTEMI prevalence of 6.8% (33/487) in patients with RD compared with 1.3% (35/2767) in patients with normal renal function. Also, cardiac causes other than coronary artery disease were more common in patients with RD and noncardiac causes less common compared with patients with normal renal function. Disagreement between the 2 independent cardiologists adjudicating the final diagnosis was more common in patients with RD compared with patients with normal renal function (13.1% versus 9.1%, *P*=0.006).

Table 1. Baseline Characteristics of Patients in Dataset A

	Normal Renal Function	Renal Dysfunction*		Renal Dysfunction (n=487)		
				NSTEMI		
	n=2767	n=487	*P* Value†	Yes (n=151)	No (n=336)	*P* Value‡
Age, y	58 (47, 70)	79 (73, 84)	<0.001	81 (75, 86)	78 (72, 83)	0.001
Sex, male	1924 (70)	284 (58)	<0.001	93 (62)	191 (57)	0.326
Risk factors						
Hypertension	1554 (56)	347 (71)	<0.001	140 (93)	299 (89)	0.202
Hypercholesterolemia	1258 (45)	347 (71)	<0.001	117 (77)	230 (68)	0.042
Diabetes mellitus	434 (16)	136 (28)	<0.001	51 (34)	85 (25)	0.054
Current smoking	770 (28)	44 (9)	<0.001	19 (13)	25 (7)	0.067
History of smoking	1001 (36)	223 (46)	<0.001	69 (46)	154 (46)	0.977
History						
Coronary artery disease	811 (29)	280 (57)	<0.001	102 (68)	178 (53)	0.003
Previous myocardial infarction	576 (21)	204 (42)	<0.001	82 (54)	122 (36)	<0.001
Previous revascularization	695 (25)	209 (43)	<0.001	73 (48)	136 (40)	0.105
Peripheral artery disease	110 (4)	62 (13)	<0.001	26 (17)	36 (11)	0.046
Previous stroke	123 (4)	58 (12)	<0.001	23 (15)	35 (10)	0.129
Vital status						
Heart rate, bpm	76 (66, 89)	75 (64, 91)	0.519	81 (70, 97)	73 (63, 88)	0.001
Systolic blood pressure, mm Hg	142 (127, 158)	138 (121, 156)	0.001	135 (123, 157)	139 (121, 156)	0.556
Diastolic blood pressure, mm Hg	82 (73, 92)	73 (64, 84)	<0.001	73 (63, 83)	74 (64, 85)	0.549
Body mass index, kg/m^2	26 (24, 30)	27 (24, 30)	0.285	26 (23, 28)	27 (25, 31)	<0.001
Electrocardiographic findings						
Left bundle-branch block	76 (3)	48 (10)	<0.001	21 (14)	27 (8)	0.044
ST-segment depression	192 (7)	74 (15)	<0.001	38 (25)	36 (11)	<0.001
T-wave inversion	288 (10)	84 (17)	<0.001	37 (25)	47 (14)	0.004
Laboratory measurements						
Serum creatinine, µmol/l	73 (63, 83)	118 (101, 140)	<0.001	123 (106, 151)	116 (99, 135)	0.002
Estimated GFR ml/min/1.73 m^2	93 (81, 104)	48 (37, 55)	<0.001	45 (34, 52)	49 (39, 55)	<0.001
Hours since CPO	5 (2, 14)	6 (3, 12)	0.018	6 (3, 12)	6 (3, 14)	0.417
Distribution of time since CPO						
≤2 h after CPO	731 (27)	97 (20)	0.002	35 (23)	62 (19)	0.550
≤3 h after CPO	1031 (37)	144 (30)	<0.001	47 (32)	97 (29)	
>3 h to ≤6 h after CPO	561 (20)	117 (24)	0.060	37 (25)	80 (24)	
>6 h after CPO	1158 (42)	226 (46)	0.146	67 (44)	159 (47)	

CPO indicates chest pain onset; GFR, glomerular filtration rate; and NSTEMI, non–ST-segment elevation myocardial infarction. Categorical variables are presented as numbers (%); continuous variables are presented as medians (quartile 1, quartile 3). Continuous variables were compared with the Mann-Whitney U test and categorical variables using the Pearson chi-square test or Fisher exact test as appropriate.

*Renal dysfunction was diagnosed if the estimated GFR was <60 mL/min/1.73 m^2 using the chronic kidney disease epidemiology collaboration formula based on plasma creatinine levels obtained at presentation to the emergency department, age, sex, and ethnicity.

†For comparisons between patients with normal renal function and renal dysfunction.

‡For comparisons between patients with and without acute myocardial infarction in the subset of patients with renal dysfunction.

Hs-cTn Concentrations at Presentation and 1-Hour Changes According to Renal Function and Final Diagnosis

In patients with RD and patients with normal renal function, hs-cTn concentrations at presentation as well as absolute 1-hour changes were significantly higher in NSTEMI compared with other final diagnoses (*P*<0.001 for all comparisons, data not shown).

In patients with final diagnoses other than NSTEMI, hs-cTnT and hs-cTnI concentrations at presentation as well as absolute 1-hour changes showed a strong, inverse correlation with eGFR, which was not observed in NSTEMI (Figure III in the online-only Data Supplement).

Table 2. Performance of the European Society of Cardiology 0/1-Hour Algorithm in Patients With Renal Dysfunction and Normal Renal Function

Using High-Sensitivity Cardiac Troponin T	Renal Dysfunction (n=487)	Normal Renal Function (n=2767)	*P* Value*
Prevalence of NSTEMI	31	13	<0.001
Sensitivity of rule-out	100.0 (97.6–100.0)	99.2 (97.6–99.8)	0.559
NPV of rule-out	100.0 (n.a.)	99.8 (99.5–100.0)	1.0
Specificity of rule-in	88.7 (84.8–91.9)	96.5 (95.7–97.2)	<0.001
PPV of rule-in	76.5 (70.6–81.6)	77.1 (73.1–80.7)	0.886
Proportion ruled out	18.1 (14.6–21.6)	67.9 (66.4–69.6)	<0.001
Based on 0-hour sample only	1.4 (0.4–2.6)	17.9 (16.6–19.3)	<0.001
Based on 0/1-hour samples	16.6 (13.5–20.0)	50.0 (48.2–51.9)	<0.001
Proportion ruled in	33.3 (29.3–37.5)	13.3 (12.0–14.6)	<0.001
Based on 0-hour sample only	25.9 (22.4–29.7)	8.0 (7.0–9.0)	<0.001
Based on 1-hour change	7.4 (5.2–9.6)	5.3 (4.5–6.1)	0.066
Overall efficacy	51.3 (46.8–55.8)	81.2 (79.8–82.6)	<0.001
Prevalence of NSTEMI in the observational group	11 (7–15)	15 (12–18)	0.186

Numbers represent percentage (95% confidence interval).

n.a. indicates not applicable; NPV, negative predictive value; NSTEMI, non–ST-segment elevation myocardial infarction; and PPV, positive predictive value. *Performances measures in patients with renal dysfunction and normal renal function were compared using the chi-square or Fisher exact test.

The diagnostic accuracy of hs-cTnT and hs-cTnI concentrations at presentation for NSTEMI, as quantified by the areas under the receiver operating characteristics curve, was high among patients with RD (for hs-cTnT, 0.87 [95% CI, 0.84–0.90]; for hs-cTnI, 0.86 [95% CI, 0.83–0.90]) but even significantly higher in patients with normal renal function (for hs-cTnT, 0.94 [95% CI, 0.93–0.95]; for hs-cTnI, 0.93 [95% CI, 0.92–0.95]) (Figure IV in the online-only Data Supplement). Smaller differences were observed for the diagnostic accuracy of the absolute 1-hour change in hs-cTn.

Performance of the ESC 0/1-Hour Algorithm Using hs-cTnT in RD

Safety of rule-out by the ESC 0/1-hour algorithm, quantified as the sensitivity for NSTEMI in the rule-out group, was high in patients with RD and similar to

Table 3. Performance of the European Society of Cardiology 0/1-Hour Algorithm in Patients With Renal Dysfunction and Normal Renal Function

Using High-Sensitivity Cardiac Troponin I	Renal Dysfunction (n=445)	Normal Renal Function (n=2504)	*P* Value
Prevalence of NSTEMI	32	13	<0.001
Sensitivity of rule-out	98.6 (95.0–99.8)	98.5 (96.5–99.5)	1.0
NPV of rule-out	97.4 (90.5–99.4)	99.7 (99.2–99.9)	0.046
Specificity of rule-in	84.4 (79.9–88.3)	91.7 (90.5–92.9)	<0.001
PPV of rule-in	70.8 (64.8–76.2)	60.7 (57.1–64.2)	0.023
Proportion ruled out	17.5 (13.9–21.4)	57.8 (55.8–59.8)	<0.001
Based on 0-hour sample only	1.3 (0.4–2.5)	10.9 (9.7–12.1)	<0.001
Based on 0/1-hour samples	16.2 (12.7–19.7)	46.9 (44.7–48.9)	<0.001
Proportion ruled in	36.2 (31.6–40.8)	18.3 (16.8–19.8)	<0.001
Based on 0-hour sample only	27.0 (23.1–30.9)	12.9 (11.5–14.2)	<0.001
Based on 1-hour change	9.2 (6.5–12.0)	5.4 (4.6–6.4)	0.002
Overall efficacy	53.5 (49.2–58.0)	76.1 (74.5–77.8)	<0.001
Prevalence of NSTEMI in the observational group	13 (9–18)	8 (6–10)	0.021

Numbers represent percentage (95% confidence interval).

n.a. indicates not applicable; NPV, negative predictive value; NSTEMI, non–ST-segment elevation myocardial infarction; and PPV, positive predictive value. *Performances measures in patients with renal dysfunction and normal renal function were compared using the chi-square or Fisher exact test.

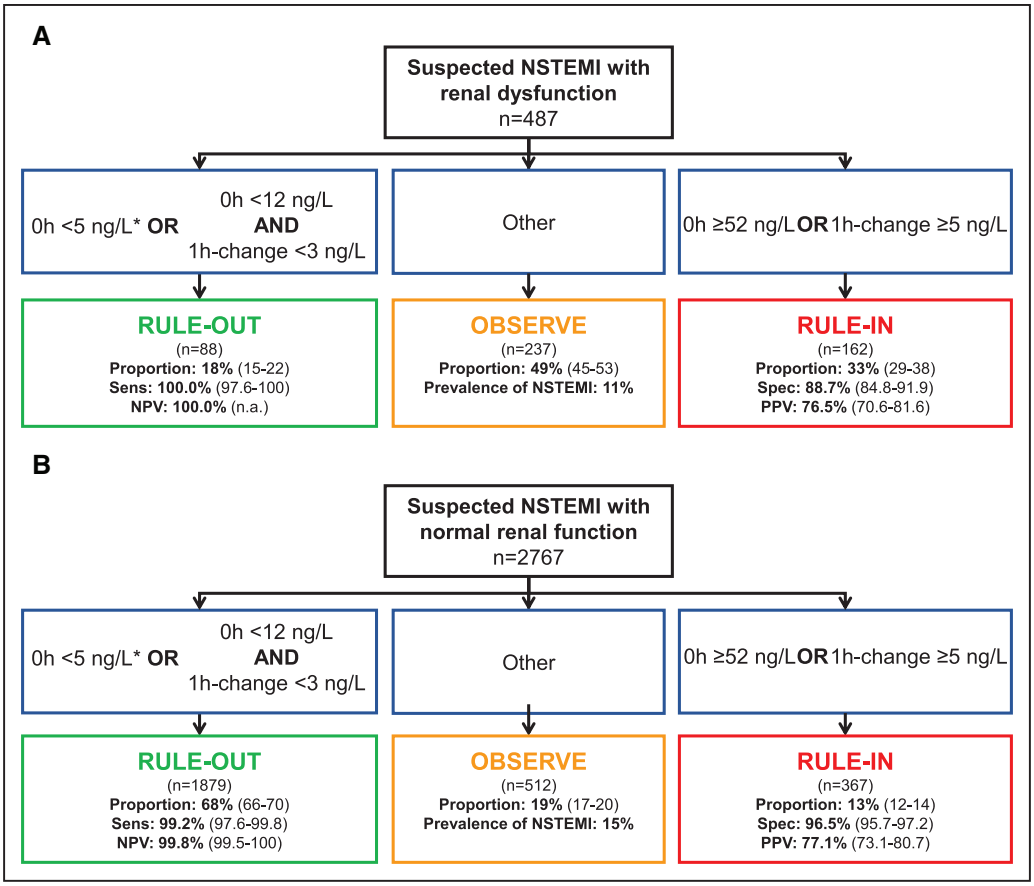


Figure 1. Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin T in patients with renal dysfunction and normal renal function.
Flow charts depicting the diagnostic performance of the European Society of Cardiology 0/1-hour algorithm for rule-out and rule-in of non–ST-segment elevation myocardial infarction in (**A**) patients with renal dysfunction (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2), and (**B**) patients with normal renal function using high-sensitivity cardiac troponin T (hs-cTnT, Elecsys analyzer). 1h-change indicates absolute (unsigned) change of high-sensitivity cardiac troponin within 1 hour; n.a., not applicable; NPV, negative predictive value; NSTEMI, non–ST-segment elevation myocardial infarction; PPV, positive predictive value; Sens, Sensitivity; and Spec, specificity. *If chest pain onset >3 hours before presentation to the emergency department.

patients with normal renal function using hs-cTnT (100% [95% CI, 97.6–100] versus 99.2% [95% CI, 97.6–99.8], respectively; *P*=0.559) (Table 2 and Figure 1). NPV was 100% in patients with RD compared with 99.8% (95% CI, 99.5–100) in patients with normal renal function (*P*=1.0).

Accuracy of rule-in, quantified as the specificity for NSTEMI in the rule-in group, was lower in patients with RD compared with patients with normal renal function (88.7% [95% CI, 84.8–91.9] versus 96.5% [95% CI, 95.7–97.2], *P*<0.001). Because of the higher prevalence of NSTEMI in patients with RD, accuracy of rule-in as quantified by PPV remained comparable in patients with RD and patients with normal renal function (PPV, 76.5% [95% CI, 70.6–81.6] versus 77.1% [95% CI, 73.1–80.7], *P*=0.886). Unstable angina (n=2 and 1), myocarditis (n=0 and 14), Tako-Tsubo cardiomyopathy (n=1 and 4), and acute heart failure (n=11 and 6) accounted for 37% and 30% of non-NSTEMI diagnoses in the rule-in groups of patients with RD and normal renal function, respectively (*P*=0.445 for comparison).

Efficacy of rule-out, quantified as the proportion of patients assigned toward rule-out based on the 0- and 1-hour samples, was substantially lower in patients with RD compared with patients with normal renal function (18.1% [95% CI, 14.6–21.6] versus 67.9% [95% CI, 66.4–69.6], *P*<0.001). Direct rule-out, based on a single hs-cTn concentration measured at presentation in patients presenting >3 hours after chest pain onset, was feasible in 1.4% (95% CI, 0.4–2.6) of patients with RD compared with 17.9% (95% CI, 16.6–19.3) of patients with normal renal function (*P*<0.001). Efficacy of rule-in was substantially higher in patients with RD compared with patients with normal renal function (33.3% [95% CI, 29.3–37.5] versus

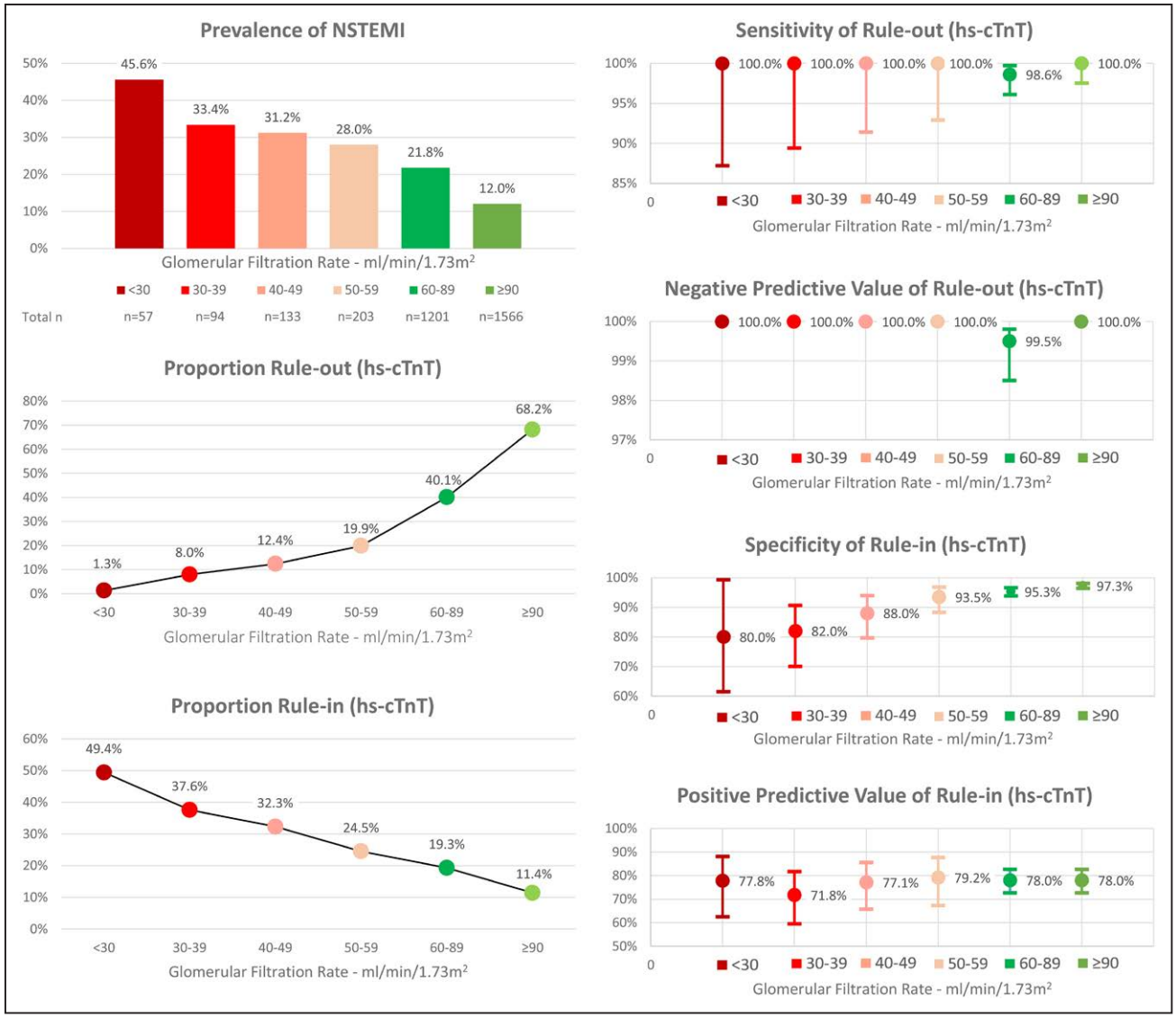


Figure 2. Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin T in different stages of renal function.
hs-cTnT indicates high-sensitivity cardiac troponin T; and NSTEMI, non–ST-segment elevation myocardial infarction.

13.3% [95% CI, 12.0–14.6], *P*<0.001). Overall efficacy, quantified as the proportion of patients assigned to either rule-out or rule-in in ≤1 hour, was substantially lower in patients with RD compared with patients with normal renal function (51.3% [95% CI, 46.8–55.8] versus 81.2% [95% CI, 79.8–82.6], *P*<0.001). Prevalence of NSTEMI in the observe group was comparable in patients with RD compared with patients with normal renal function (11% versus 15%, *P*=0.186). No NSTEMI patient with RD was incorrectly ruled out by the ESC 0/1-hour algorithm, whereas 3 NSTEMI patients (0.1%) with normal renal function were missed (Table VII in the online-only Data Supplement). The diagnostic performance of the ESC hs-cTnT 0/1-hour algorithm according to different stages of renal dysfunction is depicted in Figure 2.

Performance of the ESC 0/1-Hour Algorithm Using hs-cTnI in RD

Safety of rule-out by the ESC 0/1-hour algorithm was high in patients with RD and similar to patients with normal renal function using hs-cTnI (98.6% [95% CI, 95.0–99.8] versus 98.5% [95% CI, 96.5–99.5], respectively; *P*=1.0) (Table 3 and Figure 3). NPV (and the prevalence of non-NSTEMI) was lower in patients with RD (NPV, 97.4% [95% CI, 90.5–99.4]) compared with patients with normal renal function (NPV, 99.7% [95% CI, 99.2–99.9], *P*=0.046).

Accuracy of rule-in as quantified by specificity was lower in patients with RD compared with patients with normal renal function (specificity, 84.4% [95% CI, 79.9–88.3] versus 91.7% [95% CI, 90.5–92.9], *P*<0.001).

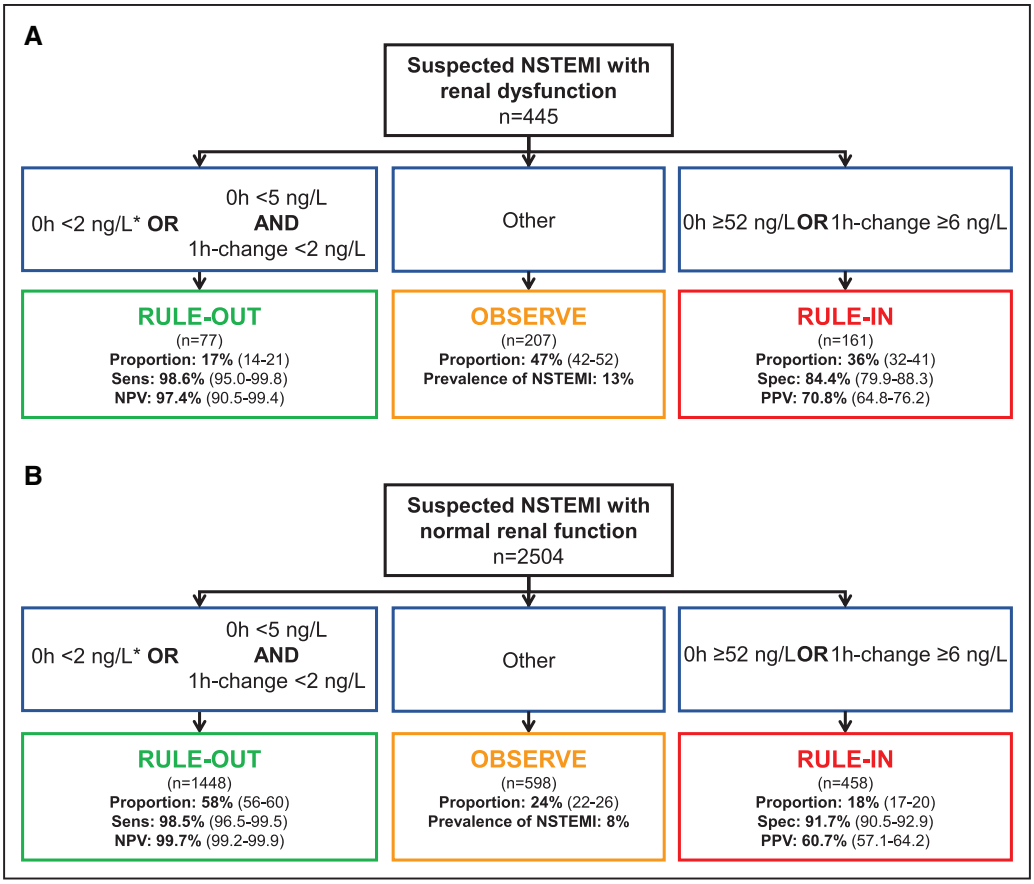


Figure 3. Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin I in patients with renal dysfunction and normal renal function.
Flow charts depicting the diagnostic performance of the European Society of Cardiology 0/1-hour algorithm for rule-out and rule-in of non–ST-segment elevation myocardial infarction in patients with (**A**) renal dysfunction and (**B**) normal renal function using high-sensitivity cardiac troponin I (hs-cTnI, Architect analyzer). 1-h change indicates absolute (unsigned) change of high-sensitivity cardiac troponin within 1 hour; NPV, negative predictive value; NSTEMI, non–ST-segment elevation myocardial infarction; PPV, positive predictive value; Sens, sensitivity; and Spec, specificity. *If chest pain onset >3 hours before presentation to the emergency department.

However, because of the higher prevalence of NSTEMI in patients with RD, accuracy as quantified by PPV of rule-in was higher in patients with RD compared with patients with normal renal function (PPV, 70.8% [95% CI, 64.8–76.2] versus 60.7% [95% CI, 57.1–64.2], *P*=0.023). Unstable angina (n=8 and 30), myocarditis (n=0 and 15), Tako-Tsubo cardiomyopathy (n=1 and 4), and acute heart failure (n=10 and 15) accounted for 40% and 36% of non-NSTEMI diagnoses in the rule-in groups of patients with RD and patients with normal renal function, respectively (*P*=0.614 for comparison).

Efficacy of rule-out was substantially lower in patients with RD compared with patients with normal renal function (17.5% [95% CI, 13.9–21.4] versus 57.8% [95% CI, 55.8–59.8], *P*<0.001). Direct rule-out was feasible in 1.3% (95% CI, 0.4–2.5) of patients with RD compared with 10.9% (95% CI, 9.7–12.1) of patients with normal renal function (*P*<0.001). Efficacy of rule-in was higher in patients with RD compared with patients with normal renal function (36.2% [95% CI, 31.6–40.8] versus 18.3% [95% CI, 16.8–19.8], *P*<0.001). Overall efficacy was substantially lower in patients with RD compared with patients with normal renal function (53.5% [95% CI, 49.2–58.0] versus 76.1% [95% CI, 74.5–77.8], *P*<0.001). Prevalence of NSTEMI in the observational group was lower in patients with RD compared with patients with normal renal function (13% versus 18%, *P*=0.021). Two patients with NSTEMI (0.4%) with RD were incorrectly ruled out by the ESC 0/1-hour algorithm, whereas 5 patients with NSTEMI (0.2%) with normal renal function were missed (Table VIII in the online-only Data Supplement). Diagnostic performance of the ESC hs-cTnI 0/1-hour algorithm according to different stages of RD is depicted in Figure 4.

Performance of the ESC 0/1-Hour Algorithm in Different Subgroups

Robust and highly comparable findings were observed in subgroup and sensitivity analyses performed in pa-

Figure 4. Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin I in different stages of renal function.

hs-cTnI indicates high-sensitivity cardiac troponin I; and NSTEMI, non–ST-segment elevation myocardial infarction.

tients presenting within the first 2 hours after chest pain onset, in patients with preexisting and new-onset of renal dysfunction, and in women and men as well as in the study dataset after exclusion of patients who were part of the original derivation cohorts of the 2 investigated 0/1-hour algorithms. Details on the diagnostic performance of the ESC 0/1-hour algorithms in the various subgroups are listed in Tables IX–XII in the online-only Data Supplement.

Modifications of the 0/1-Hour Algorithm to Optimize Rule-Out Efficacy and Rule-In Specificity in Patients With RD

Stepwise increase of the official ESC assay-specific cutoff criteria for rule-out of NSTEMI resulted in increasing rule-out efficacy, however at the cost of rule-out safety. Stepwise increase of the official ESC assay-specific cutoff criteria for rule-in of NSTEMI resulted in increasing specificity of rule-in, however at the cost of rule-in efficacy (Tables XIII and XIV in the online-only Data Supplement). Among the numerous possible cutoff criteria combinations, 1 specific cutoff value combination for rule-out, preserving the same sensitivity as the official ESC cutoff value combination, as well as 1 specific cutoff value combination for rule-in, was chosen for each hs-cTn assay to compare its performance with the official ESC 0/1-hour algorithm (Table XV and Figures V and VI in the online-only Data Supplement). Cutoff concentrations optimized for RD increased rule-out efficacy and rule-in specificity by 4.5% ($P<0.001$) and 3.9% ($P<0.001$), respectively, for hs-cTnT and by 4.7% ($P<0.001$) and 3.7%, ($P=0.001$) respectively, for hs-cTnI. However, because improved

rule-in specificity was obtained at the cost of rule-in efficacy, overall efficacy could not be optimized with the modified 0/1-hour algorithm (for hs-cTnT, −1.0%, *P*=0.568; for hs-cTnI, +1.1%, *P*=0.500).

Prognostic Performance of the ESC 0/1-Hour Algorithm

Median follow-up time was 749 days (418, 847). Estimated overall-survival was 99.2% at 30 days and 94.3% at 2 years. Particularly in patients with RD, the ESC 0/1-hour algorithm using hs-cTnT and hs-cTnI allowed a powerful discrimination between high versus moderate and low probability of short-term (30 days) and midterm (2 years) overall survival and short-term (30 days) MACE-free survival in the respective rule-out, observe, and rule-in groups (all log-rank *P* values <0.001) (Figure 5 and Figure VII in the online-only Data Supplement).

DISCUSSION

This prospective, multicenter diagnostic study enrolling unselected patients presenting with acute chest discomfort to the ED used central adjudication to assess the performance of the ESC 0/1-hour algorithm in patients with RD. We report 8 major findings.

First, patients with RD presenting with acute chest discomfort to the ED had NSTEMI >2 times as often and type 2 NSTEMI even >5 times as often as patients with normal renal function. This observation extends and corroborates previous studies indicating that RD is not only commonly associated with coronary artery disease but also hypertensive heart disease and other structural cardiac disorders prone to developing the triggers of type 2 myocardial infarction, such as tachyarrhythmias, hypertension, and anemia.[8–10,36,37]

Second, hs-cTn concentrations at presentation and their absolute 1-hour changes correlated strongly and inversely with eGFR in patients with diagnoses other than NSTEMI but not NSTEMI. Third, in patients with RD, the diagnostic performance of hs-cTn concentrations at presentation was high (areas under the receiver operating characteristics curve, 0.86–0.87) and further increased on using absolute 1-hour hs-cTn changes (areas under the receiver operating characteristics curve, 0.88–0.92).

Fourth, and likely of utmost importance, the safety of the official ESC 0/1-hour algorithm was high in patients with RD (sensitivity, 98.6–100) and comparable to patients with normal renal function (sensitivity, 98.5–99.2) irrespective of whether hs-cTnT or hs-cTnI was used. However, the efficacy of rule-out was substantially reduced in patients with RD and allowed the early rule-out in 18% of patients only.

Fifth, because of the higher proportions of patients with elevated levels of hs-cTn even in the absence of NSTEMI, specificity of rule-in was lower in patients with RD (84.4–88.7) compared with patients with normal renal function (91.7–96.5). However, the higher prevalence of NSTEMI in patients with RD also increased rule-in efficacy while maintaining high PPV of rule-in. The performance measures (mainly the PPV) of the ESC hs-cTnT 0/1-hour algorithm and the ESC hs-cTnI 0/1-hour algorithm showed subtle but consistent differences to the advantage of hs-cTnT. These differences are at least in part caused by the fact that serial measurements of hs-cTnT but not hs-cTnI were part of the extensive clinical information available for the adjudication of the final diagnosis in all patients. Accordingly, our methodology provided the most accurate and valid estimates for the ESC hs-cTnT 0/1-hour algorithm but possibly slightly underestimated the true performance of the ESC hs-cTnI 0/1-hour algorithm.

Sixth, overall efficacy allowing triage toward rule-out or rule-in based on the 0/1-hour samples was substantially reduced in patients with RD (51.3–53.5) compared with patients with normal renal function (76.1–81.2). This difference was driven by the substantial reduction in rule-out efficacy that could only partly be compensated for by the increase of rule-in efficacy. As a consequence, the percentage of patients remaining in the observe zone and usually requiring additional diagnostic tests including a 3-hour sample of hs-cTn and cardiac imaging is nearly twice as high in patients with RD compared with patients with normal renal function.

Seventh, using slightly higher cutoff concentrations of hs-cTn as an attempt to increase rule-out efficacy and rule-in specificity only partly helped to overcome the challenges posed by RD. The high pretest probability for NSTEMI in patients with RD challenges the derivation of an alternative 0/1-hour algorithm that would balance rule-out efficacy and rule-in specificity substantially better than the official ESC 0/1-hour algorithm without losing safety. It is a matter of debate how much increase of rule-out efficacy at the cost of rule-out safety or how much increase of rule-in specificity at the cost of rule-in efficacy would be acceptable. The use of alternative cutoff criteria combinations yielded rather small improvements even though they were tested in a derivation setting unblinded to the outcome NSTEMI. Accordingly, the observed small improvements in efficacy when using alternative cutoffs are associated with a potential systematic bias toward overestimating the real improvements, which might be even smaller in subsequent external validation in an independent study. Therefore, and because safety and simplicity are the most important characteristics of any diagnostic algorithm, the findings of this study recommend the use of the official ESC 0/1-hour algorithm in patients with RD until information technology-based decision tools integrating all available information (eg, age, sex, serial hs-cTn measurements, renal function) become

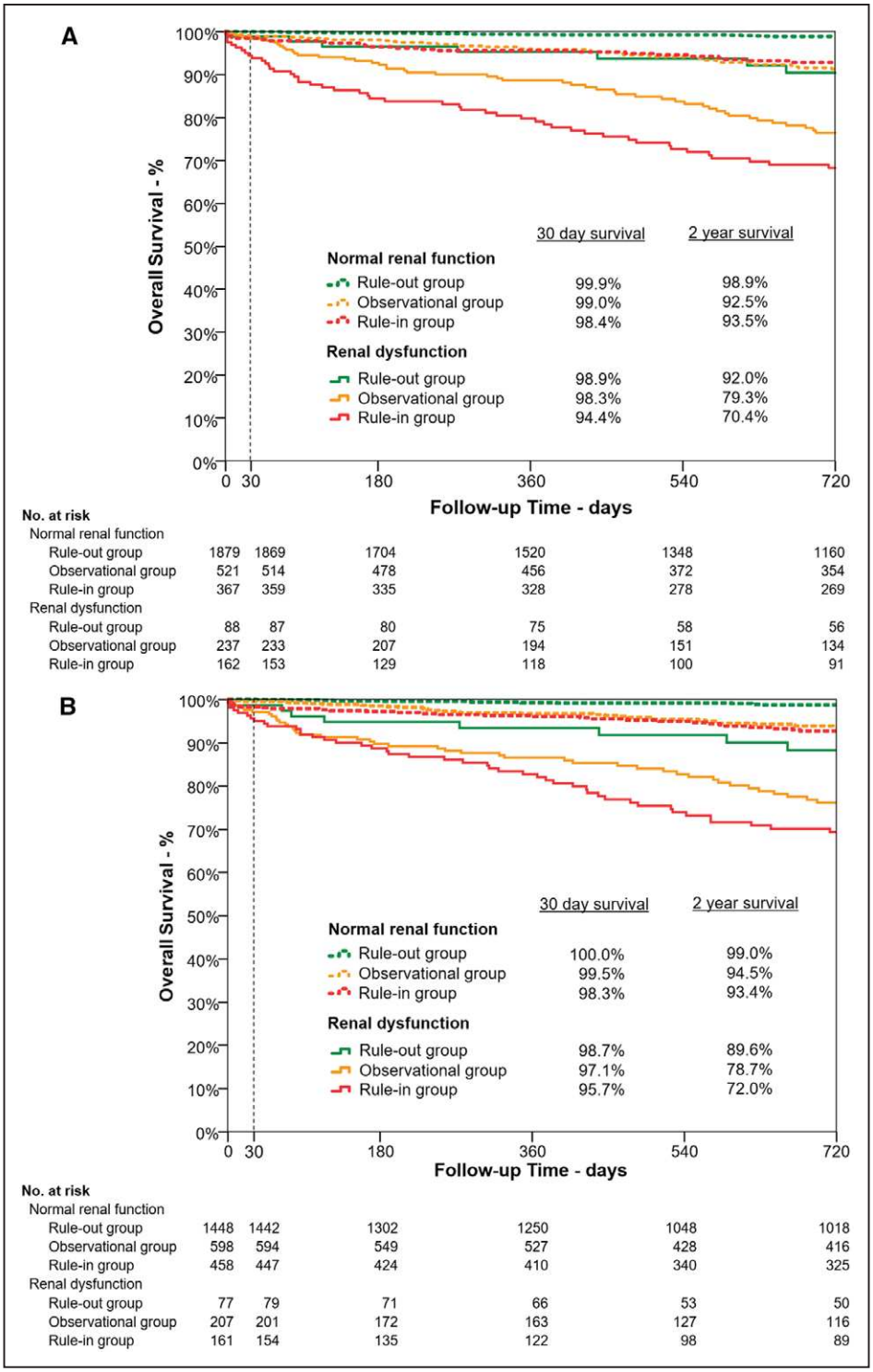


Figure 5. Short- and midterm survival according to risk stratification group by the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin T and I in patients with normal renal function and renal dysfunction.

Kaplan-Meier curves depicting overall survival within 30 and 720 days for patients with normal renal function (dashed lines) and renal dysfunction (solid lines) stratified by the European Society of Cardiology 0/1-hour algorithm to the rule-out (green lines), observational (orange lines), and rule-in (red lines) groups. **A,** Using high-sensitivity cardiac troponin T. **B,** Using high-sensitivity cardiac troponin I.

available in clinical routine. The PPV for NSTEMI in patients assigned toward rule-in and thereby early coronary angiography would still be considered high enough by most experts, particularly given the difficulty of obtaining similar diagnostic certainty in patients with moderate elevations in cTn without coronary angiography.

Eighth, the ESC 0/1-hour algorithm allowed a powerful discrimination between high versus moderate and lower probability of short- and midterm overall survival as well as short-term MACE-free survival in the respective rule-out, observe, and rule-in groups also in patients with RD. The rather high rate of all-cause mortality during follow-up and MACE within 30 days of patients in the observe zone can be explained by the high incidence of chronic diseases in those patients, such as chronic heart failure, which are associated with high rates of both overall mortality and MACE within 30 days. These findings extend and corroborate previous studies addressing the multitude of major unmet clinical needs in the often elderly patients with RD.[8–10,38]

Many of these challenges are related to the high prevalence of common yet undiagnosed cardiac comorbidities including hypertensive heart disease and diabetic cardiomyopathy associated with chronic cardiomyocyte injury and therefore increases in hs-cTn plasma concentrations and an increased prevalence of ECG abnormalities in patients with RD. The exact underlying pathophysiological mechanisms are incompletely understood. The contribution of cardiomyocyte injury to elevated plasma concentrations of hs-cTn in RD seems to be far greater than that of impaired renal clearance, particularly because the molecular size of the intact molecule is too large to be filtrated by glomeruli.[36,37,39–41] Although cTn molecules may be degraded into smaller fragments that are small enough to be filtered by the kidney,[42] the renal elimination and half-life of these cTn fragments seem to be similar in patients with RD and patients with normal renal function.[43] In addition, in patients with end-stage renal disease and only minimal remaining endogenous renal function, successful renal transplantation leads to a substantial reduction and often normalization of serum creatinine but no relevant change in plasma concentrations of cTnI.[39] It has been hypothesized that the underlying mechanism of chronic cTn release is associated with a cardiorenal syndrome triggered by some inflammatory processes leading to chronic cardiomyocyte injury and cTn release in RD.[44,45]

Initial pilot studies evaluating the use of single cutoff concentrations suggested that in patients with RD, adjusted higher hs-cTn concentrations might provide a better balance between sensitivity and specificity compared with the 99th percentiles or the optimal single-cutoff concentration derived in patients with normal renal function.[10] Meanwhile, the clinical use of hs-cTn has advanced, and current guidelines recommend the integrated use of baseline hs-cTn concentrations and their absolute changes during serial sampling, as incorporated in the ESC 0/1-hour algorithm.[1] In contrast to a single cutoff strategy, the ESC 0/1-hour algorithm triages patients toward 1 of 3 strata: rule-out, observe, or rule-in. Assessing the possible use of adjusted higher hs-cTn concentrations within this state-of-the-art concept in patients with RD revealed pros and cons.

To the best of our knowledge, this is the first study investigating in detail the diagnostic performance of the ESC 0/1-hour algorithm in the vulnerable patient population with RD, extending the excellent performance characteristics observed in patients with overwhelmingly normal renal function.[16–21] We cannot generalize our findings to patients with terminal kidney failure on chronic dialysis because they were excluded from this study. Additionally, our study was conducted in patients at the ED with symptoms suggestive of AMI. Further studies are required to quantify the utility of the ESC 0/1-hour algorithm in patients with either higher (eg, in a coronary care unit setting) or lower (eg, in a general practitioner setting) pretest probability for AMI.

Some limitations merit consideration when interpreting these findings. First, although we used the most stringent methodology to adjudicate the presence or absence of NSTEMI, including central adjudication by experienced cardiologists, imaging, and serial measurements of hs-cTn, we still may have misclassified a small number of patients.[3,14] Second, to reflect the clinical information available to the ED physician when interpreting hs-cTn concentrations, we classified RD according to eGFR based on the serum creatinine concentrations obtained at ED presentation. Accordingly, this classification differs from the definition of chronic kidney disease, which would require RD to be present for 3 months.[46] Third, the chronic kidney disease epidemiology collaboration formula was used to estimate GFR irrespective of age. However, the chronic kidney disease epidemiology collaboration formula was primarily validated in patients <70 years of age.

In conclusion, in patients with RD, the safety of the ESC 0/1-hour algorithm is high, but the specificity of rule-in and overall efficacy are decreased. Modifications of cutoffs can only partly overcome the challenges of RD.

AUTHORS

Raphael Twerenbold, MD; Patrick Badertscher, MD; Jasper Boeddinghaus, MD; Thomas Nestelberger, MD; Karin Wildi, MD; Christian Puelacher, MD; Zaid Sabti, MD; Maria Rubini Gimenez, MD; Sandra Tschirky, MD; Jeanne du Fay de Lavallaz, MD; Nikola Kozhuharov, MD; Lorraine Sazgary, MD; Deborah Mueller, MD; Tobias Breidthardt, MD; Ivo Strebel, MS; Dayana Flores Widmer, MD; Samyut Shrestha, MD; Òscar Miró, MD; F. Javier Martín-Sánchez, MD; Beata Morawiec, MD; Jiri Parenica, MD; Nicolas Geigy, MD; Dagmar I. Keller, MD; Katharina Rentsch, PhD; Arnold von Eckardstein, MD; Stefan Osswald, MD; Tobias Reichlin, MD; Christian Mueller, MD

SOURCES OF FUNDING

This work was supported by research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the Kommission für Technologie und Innovation, the Stiftung für kardiovaskuläre Forschung Basel, Abbott, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, and Singulex.

DISCLOSURES

The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the paper, and decided to publish. Drs Twerenbold and Mueller had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors have read and approved the manuscript. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the manuscript. The manuscript and its contents have not been published previously and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers. Dr Twerenbold received research support from the Swiss National Science Foundation (P300PB_167803), the University Hospital Basel, the University of Basel, and the Cardiovascular Research Foundation Basel, as well as speaker honoraria/consulting honoraria from Abbott, Brahms, Siemens, Singulex, and Roche. Dr Boeddinghaus received speaker honoraria from Siemens. Dr Rubini received speaker honoraria from Abbott and research grants from the Swiss Heart Foundation. Dr Reichlin received research grants from the Goldschmidt-Jacobson-Foundation, the Swiss National Science Foundation (PASMP3-136995), the Swiss Heart Foundation, the Professor Max Cloëtta Foundation, the Uniscientia Foundation Vaduz, the University of Basel, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria from Brahms and Roche. Dr Mueller received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the Kommission für Technologie und Innovation, the Stiftung für kardiovaskuläre Forschung Basel, Abbott, Alere, AstraZeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Sphingotec, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Alere, AstraZeneca, Biomerieux, Boehringer Ingelheim, Bristol-Myers Squibb, Brahms, Cardiorentis, Novartis, Roche, Siemens, and Singulex. The other authors report no conflicts.

The investigated hs-cTn assays were donated by the manufacturers, which had no role in the design of the study, analysis of the data, preparation of the manuscript, or decision to submit the manuscript for publication.

AFFILIATIONS

Cardiovascular Research Institute Basel and Department of Cardiology, University Hospital Basel, University of Basel, Switzerland (R.T., P.B., J.B., T.N., K.W., C.P., Z.S., M.R.G., S.T., J.d.F.d.L., N.K., L.S., D.M., T.B., I.S., D.F.W., S.S., S.O., T.R., C.M.). Department of General and Interventional Cardiology, University Heart Center Hamburg, University Hospital Hamburg-Eppendorf, Germany (R.T.). Emergency Department, Hospital Clinic, Barcelona, Spain (O.M.). Emergency Department, Hospital Clinico San Carlos, Madrid, Spain (F.J.M.S.). 2nd Cardiology Department, Zabrze, University Silesia, Katowice, Poland (B.M.). Department of Cardiology, University Hospital Brno, Czech Republic (J.P.). Medical Faculty, Masaryk University, Brno, Czech Republic (J.P.). Emergency Department, Kantonsspital Liestal, Switzerland (N.G.). Emergency Department, University Hospital Zürich, Switzerland (D.I.K.). Department of Laboratory Medicine, University Hospital Basel, Switzerland (K.R.). Department of Laboratory Medicine, University Hospital Zürich, Switzerland (A.v.E.).

FOOTNOTES

Received April 24, 2017; accepted October 19, 2017.

The online-only Data Supplement, podcast, and transcript are available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.028901/-/DC1.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J; Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315. doi: 10.1093/eurheartj/ehv320.
2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; Members AATF, Society for Cardiovascular A, Interventions and the Society of Thoracic S. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2354–2394. doi: 10.1161/CIR.0000000000000133.
3. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernández-Avilés F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation*. 2007;116:2634–2653. doi: 10.1161/CIRCULATIONAHA.107.187397.
4. Taylor MJ, Scuffham PA, McCollam PL, Newby DE. Acute coronary syndromes in Europe: 1-year costs and outcomes. *Curr Med Res Opin*. 2007;23:495–503. doi: 10.1185/030079906X167462.
5. Tiemann O. Variations in hospitalisation costs for acute myocardial infarction: a comparison across Europe. *Health Econ*. 2008;17(suppl 1):S33–S45. doi: 10.1002/hec.1322.

6. deFilippi CR, Herzog CA. Interpreting cardiac biomarkers in the setting of chronic kidney disease. *Clin Chem*. 2017;63:59–65. doi: 10.1373/clinchem.2016.254748.
7. Twerenbold R, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Badertscher P, Mueller C. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. *J Am Coll Cardiol*. 2017;70:996–1012. doi: 10.1016/j.jacc.2017.07.718.
8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305. doi: 10.1056/NEJMoa041031.
9. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285–1295. doi: 10.1056/NEJMoa041365.
10. Twerenbold R, Wildi K, Jaeger C, Gimenez MR, Reiter M, Reichlin T, Walukiewicz A, Gugala M, Krivoshei L, Marti N, Moreno Weidmann Z, Hillinger P, Puelacher C, Rentsch K, Honegger U, Schumacher C, Zurbriggen F, Freese M, Stelzig C, Campodarve I, Bassetti S, Osswald S, Mueller C. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. *Circulation*. 2015;131:2041–2050. doi: 10.1161/CIRCULATIONAHA.114.014245.
11. Aronow WS, Ahn C, Mercando AD, Epstein S. Prevalence of coronary artery disease, complex ventricular arrhythmias, and silent myocardial ischemia and incidence of new coronary events in older persons with chronic renal insufficiency and with normal renal function. *Am J Cardiol*. 2000;86:1142–1143.
12. Nakamura S, Uzu T, Inenaga T, Kimura G. Prediction of coronary artery disease and cardiac events using electrocardiographic changes during hemodialysis. *Am J Kidney Dis*. 2000;36:592–599. doi: 10.1053/ajkd.2000.16198.
13. deFilippi C, Seliger SL, Kelley W, Duh SH, Hise M, Christenson RH, Wolf M, Gaggin H, Januzzi J. Interpreting cardiac troponin results from high-sensitivity assays in chronic kidney disease without acute coronary syndrome. *Clin Chem*. 2012;58:1342–1351. doi: 10.1373/clinchem.2012.185322.
14. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, Huber K, Plebani M, Biasucci LM, Tubaro M, Collinson P, Venge P, Hasin Y, Galvani M, Koenig W, Hamm C, Alpert JS, Katus H, Jaffe AS; Study Group on Biomarkers in Cardiology of ESC Working Group on Acute Cardiac Care. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J*. 2012;33:2252–2257. doi: 10.1093/eurheartj/ehs154.
15. Reichlin T, Twerenbold R, Wildi K, Rubini Gimenez M, Bergsma N, Haaf P, Druey S, Puelacher C, Moehring B, Freese M, Stelzig C, Krivoshei L, Hillinger P, Jäger C, Herrmann T, Kreutzinger P, Radosavac M, Weidmann ZM, Pershyna K, Honegger U, Wagener M, Vuillomenet T, Campodarve I, Bingisser R, Miró Ò, Rentsch K, Bassetti S, Osswald S, Mueller C. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. *CMAJ*. 2015;187:E243–E252. doi: 10.1503/cmaj.141349.
16. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, Moehring B, Ziller R, Hoeller R, Rubini Gimenez M, Haaf P, Potocki M, Wildi K, Balmelli C, Freese M, Stelzig C, Freidank H, Osswald S, Mueller C. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Arch Intern Med*. 2012;172:1211–1218. doi: 10.1001/archinternmed.2012.3698.
17. Rubini Gimenez M, Twerenbold R, Jaeger C, Schindler C, Puelacher C, Wildi K, Reichlin T, Haaf P, Merk S, Honegger U, Wagener M, Druey S, Schumacher C, Krivoshei L, Hillinger P, Herrmann T, Campodarve I, Rentsch K, Bassetti S, Osswald S, Mueller C. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. *Am J Med*. 2015;128:861.e4–870.e4. doi: 10.1016/j.amjmed.2015.01.046.
18. Mueller C, Giannitsis E, Christ M, Ordóñez-Llanos J, deFilippi C, McCord J, Body R, Panteghini M, Jernberg T, Plebani M, Verschuren F, French J, Christenson R, Weiser S, Bendig G, Dilba P, Lindahl B; TRAPID-AMI Investigators. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med*. 2016;68:76.e4–87.e4. doi: 10.1016/j.annemergmed.2015.11.013.
19. Pickering JW, Greenslade JH, Cullen L, Flaws D, Parsonage W, Aldous S, George P, Worster A, Kavsak PA, Than MP. Assessment of the European Society of cardiology 0-hour/1-hour algorithm to rule-out and rule-in acute myocardial infarction. *Circulation*. 2016;134:1532–1541. doi: 10.1161/CIRCULATIONAHA.116.022677.
20. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med*. 2009;361:858–867. doi: 10.1056/NEJMoa0900428.
21. Twerenbold R, Jaeger C, Rubini Gimenez M, Wildi K, Reichlin T, Nestelberger T, Boeddinghaus J, Grimm K, Puelacher C, Moehring B, Pretre G, Schaerli N, Campodarve I, Rentsch K, Steuer S, Osswald S, Mueller C. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. *Eur Heart J*. 2016;37:3324–3332. doi: 10.1093/eurheartj/ehw232.
22. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HC, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF; STARD Group. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *Clin Chem*. 2015;61:1446–1452. doi: 10.1373/clinchem.2015.246280.
23. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
24. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem*. 2010;56:254–261. doi: 10.1373/clinchem.2009.132654.
25. Hallermayer K, Jarausch J, Menassanch-Volker S, Zaugg C, Ziegler A. Implications of adjustment of high-sensitivity cardiac troponin T assay. *Clin Chem*. 2013;59:572–574. doi: 10.1373/clinchem.2012.197103.
26. Kuster N, Dupuy AM, Monnier K, Baptista G, Bargnoux AS, Badiou S, Jeandel C, Cristol JP. Implications of adjustment of high-sensitivity cardiac troponin T assay. *Clin Chem*. 2013;59:570–572. doi: 10.1373/clinchem.2012.197020.
27. Kavsak PA, Hill SA, McQueen MJ, Devereaux PJ. Implications of adjustment of high-sensitivity cardiac troponin T assay. *Clin Chem*. 2013;59:574–576. doi: 10.1373/clinchem.2012.197434.
28. Wildi K, Twerenbold R, Jaeger C, Rubini Giménez M, Reichlin T, Stoll M, Hillinger P, Puelacher C, Boeddinghaus J, Nestelberger T, Grimm K, Grob M, Rentsch K, Arnold C, Mueller C. Clinical impact of the 2010-2012 low-end shift of high-sensitivity cardiac troponin T. *Eur Heart J Acute Cardiovasc Care*. 2016;5:399–408. doi: 10.1177/2048872616642952.
29. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. *Clin Chem*. 2012;58:1574–1581. doi: 10.1373/clinchem.2012.192716.
30. Koerbin G, Tate J, Potter JM, Cavanaugh J, Glasgow N, Hickman PE. Characterisation of a highly sensitive troponin I assay and its application to a cardio-healthy population. *Clin Chem Lab Med*. 2012;50:871–878. doi: 10.1515/cclm-2011-0540.
31. Krintus M, Kozinski M, Boudry P, Capell NE, Köller U, Lackner K, Lefèvre G, Lennartz L, Lotz J, Herranz AM, Nybo M, Plebani M, Sandberg MB, Schratzberger W, Shih J, Skadberg Ø, Chargui AT, Zaninotto M, Sypniewska G. European multicenter analytical evaluation of the Abbott ARCHITECT STAT high sensitive troponin I immunoassay. *Clin Chem Lab Med*. 2014;52:1657–1665. doi: 10.1515/cclm-2014-0107.
32. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? *Circulation*. 2013;127:2452–2457. doi: 10.1161/CIRCULATIONAHA.113.001258.
33. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36. doi: 10.1148/radiology.143.1.7063747.
34. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. *J Clin Epidemiol*. 1991;44:763–770.
35. Moskowitz CS, Pepe MS. Comparing the predictive values of diagnostic tests: sample size and analysis for paired study designs. *Clin Trials*. 2006;3:272–279. doi: 10.1191/1740774506cn147oa.
36. Irfan A, Twerenbold R, Reiter M, Reichlin T, Stelzig C, Freese M, Haaf P, Hochholzer W, Steuer S, Bassetti S, Zellweger C, Freidank H, Peter F, Campodarve I, Meune C, Mueller C. Determinants of high-sensitivity troponin T among patients with a noncardiac cause of chest pain. *Am J Med*. 2012;125:491.e1–498.e1. doi: 10.1016/j.amjmed.2011.10.031.
37. Mueller C, Laule-Kilian K, Scholer A, Nusbaumer C, Zeller T, Staub D, Perruchoud AP. B-type natriuretic peptide for acute dyspnea in patients with kidney disease: insights from a randomized comparison. *Kidney Int*. 2005;67:278–284. doi: 10.1111/j.1523-1755.2005.00079.x.

38. Reiter M, Twerenbold R, Reichlin T, Haaf P, Peter F, Meissner J, Hochholzer W, Stelzig C, Freese M, Heinisch C, Breidthardt T, Freidank H, Winkler K, Campodarve I, Gea J, Mueller C. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. *Eur Heart J*. 2011;32:1379–1389. doi: 10.1093/eurheartj/ehr033.
39. Bozbas H, Korkmaz ME, Atar I, Eroglu S, Ozin B, Yildirir A, Muderrisoglu H, Colak T, Karakayali H, Haberal M. Serum levels of cardiac enzymes before and after renal transplantation. *Clin Cardiol*. 2004;27:559–562.
40. Fridén V, Starnberg K, Muslimovic A, Ricksten SE, Bjurman C, Forsgard N, Wickman A, Hammarsten O. Clearance of cardiac troponin T with and without kidney function. *Clin Biochem*. 2017;50:468–474. doi: 10.1016/j.clinbiochem.2017.02.007.
41. van der Linden N, Cornelis T, Kimenai DM, Klinkenberg LJJ, Hilderink JM, Lück S, Litjens EJR, Peeters FECM, Streng AS, Breidthardt T, van Loon LJC, Bekers O, Kooman JP, Westermark PO, Mueller C, Meex SJR. Origin of cardiac troponin T elevations in chronic kidney disease. *Circulation*. 2017;136:1073–1075. doi: 10.1161/CIRCULATIONAHA.117.029986.
42. Diris JH, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. *Circulation*. 2004;109:23–25. doi: 10.1161/01.CIR.0000109483.45211.8F.
43. Ellis K, Dreisbach AW, Lertora JL. Plasma elimination of cardiac troponin I in end-stage renal disease. *South Med J*. 2001;94:993–996.
44. Wong CK, Szeto CC, Chan MH, Leung CB, Li PK, Lam CW. Elevation of pro-inflammatory cytokines, C-reactive protein and cardiac troponin T in chronic renal failure patients on dialysis. *Immunol Invest*. 2007;36:47–57. doi: 10.1080/08820130600745505.
45. D'Marco L, Bellasi A, Raggi P. Cardiovascular biomarkers in chronic kidney disease: state of current research and clinical applicability. *Dis Markers*. 2015;2015:586569. doi: 10.1155/2015/586569.
46. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137–147.

0/1-Hour Triage Algorithm for Myocardial Infarction in Patients With Renal Dysfunction

Raphael Twerenbold, Patrick Badertscher, Jasper Boeddinghaus, Thomas Nestelberger, Karin Wildi, Christian Puelacher, Zaid Sabti, Maria Rubini Gimenez, Sandra Tschirky, Jeanne du Fay de Lavallaz, Nikola Kozhuharov, Lorraine Sazgary, Deborah Mueller, Tobias Breidthardt, Ivo Strebel, Dayana Flores Widmer, Samyut Shrestha, Òscar Miró, F. Javier Martín-Sánchez, Beata Morawiec, Jiri Parenica, Nicolas Geigy, Dagmar I. Keller, Katharina Rentsch, Arnold von Eckardstein, Stefan Osswald, Tobias Reichlin and Christian Mueller

Circulation. 2018;137:436-451; originally published online November 3, 2017;
doi: 10.1161/CIRCULATIONAHA.117.028901
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Dr. Carolyn Lam: Welcome to Circulation On The Run. Your weekly podcast summary and backstage pass to the journal and its editors. I'm Dr. Carolyn Lam, associate editor from the National Heart Center and Duke National University of Singapore.

In just a moment, we are going to be discussing the diagnostic conundrum of elevated high sensitivity cardiac troponin levels in a patient with renal disease, but also suspected of acute coronary syndrome. Aha! I bet I caught your attention. A very, very familiar diagnostic dilemma. So stay tuned right after these summaries.

Cardiac allograft vasculopathy is the leading cause of death in patients more than five years post cardiac transplantation. It has been hypothesized that cardiac allograft vasculopathy results from interrupted lymphatic drainage post surgery. Since the donor lymphatic vessels are not inesthimozed to that of the recipient during transplantation, thus the lymphatic system may play a crucial role in the alloimmune response.

Well, these hypothesis are addressed in the first paper in today's journal from first author Dr. Edwards, corresponding author Dr. Wong and colleagues from Kings College, London. These authors use spect CT lymphoscintigraphy in a pre-clinical model. And therefore provided objective quantification of lymphatic flow following transplantation and showed that this correlated to cardiac allograft vasculopathy. They demonstrated that cardiac lymphatic remodeling and lymphatic transport dysfunction post transplant was associated with cardiac allograft vasculopathy and transplant rejection.

They further showed that lymphatic flow was increased during chronic rejection. This in turn may have resulted in enhanced trafficking of antigen presenting cells to the local draining lymph nodes in an augmented alloimmune response. Now although the cause and effect of this phenomenon could not be fully established, these data provided the impetus for the investigation of lymphangiogenesis inhibition as a means to dampen chronic rejection.

The absorb bioresorbable vascular scaffold is known to completely resolve within three years after coronary artery implantation. However, what is the safety and effectiveness of these bioresorbable scaffolds during this critical three year period. First author Dr. Ali, corresponding author Dr. Stone and colleagues from Columbia University Medical Center performed an individual patient level meta analysis of the four randomized absorb trial and demonstrated that compared with metallic everolimus eluting stents, the bioresorbable vascular scaffold had higher rates of target lesion failure and device thrombosis cumulatively to three years and between one and three years. Multi-variable analysis identified the number of treated lesions, current tobacco use and previous cardiac interventions as independent predictors of three year target lesion failure. Whereas diabetes was predictive of three year device thrombosis in bioresorbable vascular scaffold treated patients.

The next paper reported the three year follow up of the FAME 2 trial, which compared PCI guided bi-fractional flow reserve with best medical therapy in patients with stable coronary artery disease to assess clinical outcomes and cost effectiveness. First and corresponding author Dr. Fearon and colleagues from Stanford cardiovascular institute showed that major adverse cardiac events at three years were significantly lower in the PCI group, compared with the medical treatment group. This difference was primarily as a result of a lower rate of urgent revascularization. Mean initial costs were higher in the PCI group, but by three years, were similar between the two groups. The incremental cost effectiveness ratio for PCI compared to medical therapy was more than $17,000 per quality adjusted life year at two years and $1,600 per quality adjusted life year at three years. Thus the authors concluded that percutaneous coronary intervention in patients with stable coronary artery disease and at normal fractional flow reserve may be advantages compared to with medical therapy alone, because it results in improved clinical outcomes and quality of life at no increased cost by the end of three years follow up.

The next study shows for the first time, that pioglitazone may prevent stroke as a single stand-alone outcome. Today's paper by first author Dr. Yaghi, corresponding author Dr. Kernan from Yale School of Medicine and colleagues was a secondary analysis of the iris trial, which showed that pioglitazone reduced the risk for a composite outcome of stroke on myocardial infarction among non-diabetic patients with insulin resistant and a recent stroke or transient ischemic attack. Now, the current planned secondary analysis used updated American Heart Association 2013 consensus criteria for ischemic stroke to examine the effect of pioglitazone on stroke outcomes. The study found that pioglitazone reduced the risk by 25% by five years, with absolute rates of 8% with pioglitazone versus 10.7% with placebo. Pioglitazone reduced the risk for ischemic strokes, but had no effect on the risk of hemorrhagic events. These findings add to the evidence that pioglitazone may be a potent therapy for vascular disease risk reduction and may help inform shared decision making by providers and patients for the use of pioglitazone after ischemic stroke or transient ischemic attack.

Well, that ends it for our summaries. Now for a feature discussion.

The cardiac troponins have really revolutionized cardiology. We use them in of course the diagnosis of myocardial infarction and in fact the recent European Society of Cardiology recommendations say that the rapid zero and one hour triage algorithm for rule in or rule out of non STEMI should use high sensitivity troponins and interestingly irrespective of renal function. Now this latter point has caused some confusion, some questions, since we all know that patients with chronic kidney disease frequently have higher or increased levels of cardiac troponins, especially since we now can detect them with the high sensitivity essays. And this is even in the absence of an acute coronary syndrome.

Well, this week's journal contains two papers that address this topic so well. And I am delighted to have with us the corresponding author of the first paper,

Dr. Christian Mueller from University Hospital Basel in Switzerland and the author of the second paper, Dr. Nicholas Mills from University of Edinburgh in Scotland. For the more, we have Dr. Torbjorn Omland, associate editor from University of Oslo in Norway.

Lot's to talk about. Christian, could I start with you? Could you say in your own words the rationale for looking at this vulnerable population and then perhaps describe what you did in your study?

Dr. Christian Mueller: I'm very thankful that Circulation shed a lot of light on the population of patients with renal dysfunction, because both as a clinician and as a researcher, I'm definitely convinced that they merit a lot of our attention for several reasons.

So first, it's important to be aware that the incidents of acute myocardial infarction among patients presenting with acute chest pain is much higher in patients with renal dysfunction, as compared to patients with normal renal function. And second, atypical clinical presentations also are more frequent in patients with renal dysfunction. Then possibly third, the ECG of course also a mandatory tool in our assessment is more often showing unspecific signs that may mimic or obscure the presence of myocardial infarctions and most of them are related to left ventricular hypertrophy. And in addition, patients with renal dysfunction are more prone to adverse events, both related to cardiovascular medication. For example, anticoagulation as well as our cardiovascular procedures, including PCI. Now again, as both papers have a strong focus on troponin, also cardiac troponin is a bit more difficult to interpret in patients with renal dysfunction related to exactly as you mentioned chronic elevations of cardiac troponin, TNI related to chronic cardiovascular disease.

And I think that's so important to stress, any troponin signal in a patient with renal dysfunction is real and should not be incorrectly attributed to just a problem of impaired secretion by the kidneys.

Dr. Carolyn Lam: So definitely an even greater need to diagnose myocardial infarction accurately in this very high risk population. So tell us what you did.

Dr. Christian Mueller: We assessed this challenging sub group within the APACE study. So APACE is a large international prospective diagnostic study that is run in five countries with 12 centers. And we actually enroll consecutive patients presenting with suspected myocardial infarction. And then all patients get a very detailed workup and then adjudicated final diagnosis. And the adjudicated file diagnosis is done by two independent cardiologists and is based on two enormous extensive sets of data. The clinical data set that has been obtained at the local site and of course includes cardiac imaging and standard troponin testing, ECG data.

In the second set of data that includes the study specific data sets, including serial measurements with high sensitivity carry troponin essay and a lot of details characterization of patients and patient follow up. So this is the reference standard against which the one hour algorithm the European Society of Cardiology evaluated. And the one hour algorithm has been derived and previously validated in overall population. Mainly patients with normal renal function. And so we tried to evaluate the performance of this predefined algorithm specifically in patients with renal dysfunctions.

So among a bit more than 3,000 patients, the prevalence of patients with renal dysfunction was 15%. So we had about 500 patients with renal dysfunction. And the interesting finding from our work is that first the prevalence of N-STEMI was nearly threefold in patients with renal dysfunction as compared to patients with normal renal function. And, fortunately the rule out part of the algorithm regarding sensitivity still works very well. It is, however, the efficacy of rule out that is lower in patients with renal dysfunction, simply because fewer patients really have very low troponin concentration and are therefore ineligible for rule out.

However, as a clinician, the main concern with troponin and renal dysfunction is the rule in part, and specificity. And as you would think, specificity of the one hour algorithm was in fact significantly lower in patients with renal dysfunction. It was still appropriate for therapeutic consequences, but it was lower as compared to patients with normal renal function, so the specificity was 89% in patients with renal dysfunction, as compared to 96.5% in normal renal function.

So the overall efficacy of the algorithm was lower in patients with renal dysfunction, however then when trying to create and derive optimized cut off levels, so all cut off levels optimized for use in renal dysfunction, we didn't really find alternative cut offs that would do a much better job than the official cut off levels recommended in the guidelines. So our conclusion is that in patients with renal dysfunction, the safety of the one hour algorithm still is very high, however the specificity of rule in and overall efficacy are decreased.

Dr. Carolyn Lam: Right. That's beautifully summarized. And also that different cut offs didn't really help to increase the efficacy of this algorithm. And just to clarify to our listeners, I believe you defined renal dysfunction as an estimated GFR of less than 60, which is so beautiful because it's perfectly consistent with the second paper.

Nick, could you please tell us about your study and your take home messages as well.

Dr. Nicholas Mills: So high stakes is our clinical trial that we're conducting across hospitals in Scotland to evaluate the best way to use high levels of cardiac troponin in clinical practice. One of the areas of uncertainty is whether these assets really add any additional value for patients with chronic kidney disease, where troponin concentrations tend to be higher. And the premise of a high sensitive

test is that we can measure lower concentrations and improve the sensitivity. But is this just going to create uncertainty for clinicians?

So we evaluated 5,000 consecutive patients for performance of high sensitivity cardiac to put in testing. And those with and without renal impairment. And based upon what Christian, we identified that patients with renal impairment are less likely to have very low concentrations, but that you can rule out myocardial infarction safely in patients with renal impairment. And similarly that those with renal impairment are more likely to have an abnormal troponin concentration at presentation. Around about 40% of all patients have troponins above the upper reference limit. And whilst the specificity for myocardial infarction is lower, type one myocardial infarction or myocardial infarction due to plaque rupture or cardiac thrombosis remains the most common diagnosis in this group.

Finally we looked at one year outcomes. And this is really critical. Because we found that patients with renal impairment were two to threefold more likely to die from cardiovascular disease one year following their presentation than those without renal impairment. And I think that my general experience during these tests in clinical practice is that troponin elevations in patients with kidney disease are often ignored and there's a concern about what they mean, and therefore these patients don't get access to the fantastic treatments we have for coronary heart disease. So our take home message is that high sets of troponin testing in patients with renal disease does have value, it's useful for identifying low risk patients although there are fewer of them, and it performs well as a diagnostic test, highlighting in particular a group of patients that really have poor clinical outcomes.

As a cardiological community, we need to do better.

Dr. Carolyn Lam: What I really love about both or your papers is the consistency in the messages. Torbjorn, I want to bring you in on this. You managed both papers. Such a lovely pair of papers that we're so proud to be publishing and you had also invited an editorial by Dr. deFilippi and Seliger. Would you like to comment on your perspective and perhaps the clinical take home message to our audience?

Dr. Torbjørn Omland: Yes, I think this has been pointed very well out by both Christian and Nick. And I think it's worth recapitulating that renal dysfunction is a major problem that clinicians often try to explain by just lack of renal filtration. But that the closest probably are increased production and underlying cardiac disease. So in the editorial Dr. deFilippi Filippi and Dr. Seliger points also out in these things. Moreover they try to look forward and have made comments to recent studies that showed that in patients with renal dysfunction have different troponin fragments than patients with acute myocardial infarctions.

Dr. Carolyn Lam: I find that so fascinating. And it really, really relates to the field of heart failure and what we are also talking and thinking about with natriuretic peptides and

their different fragments and the possible different meanings. And how different essays maybe non specific for different fragments.

Christian, you think a lot about these things. I'm curious, what are your thoughts on this and areas of future work that are very urgent?

Dr. Christian Mueller: I think Torbjorn very nicely addressed this. So the current high sensitivity essays for T and I that we use in clinical practice, they are designed kind of to detect everything in blood that looks like troponin, either T or I, including various fragments. And I think it's a fantastic new avenue of research, trying to find out that the biochemical signatures can be further differentiated and exactly that perhaps different troponin fragments or tricordinate products more prominent in patients having ischemic injuries like treat myocardial infarction, as compared to for example other modes of injuries. So I think that's very nice hypothesis and some early data. But at least from my perspectives and to the best of my knowledge until now, the diagnostic algorithms that we have other ways to approach this in clinical practice. And so it's the higher the blood concentration in patients with acute chest pain, the more likely it's acute myocardial infarction. It's not any chronic disease and again the higher the change from presentation to one hour or two hours, the more likely it's acute as a dynamic disorder resulting in an acute increase in cardiac troponin, as compared to the chronic release patterns typically seen in patients with renal dysfunction.

Dr. Carolyn Lam: Yeah. That's just so fascinating. Nick, we sadly are running out of time, but I do want to give you the last word. The clinical take home message, once again. What do you think listeners should take home that may change their practice, after listening to this podcast?

Dr. Nicholas Mills: I think the key message for clinicians, is that in a patient with suspected acute coronary syndrome and has renal impairment and elevated troponin concentration, serial testing is mandatory to differentiate between those that have chronic myocardial injury due to subclinical heart disease and those that are having acute myocardial injury as a consequence of a presumed acute coronary syndrome. Field testing is critical to inform which treatment path and what investigations we recommend for our patients.

Dr. Carolyn Lam: Wonderful. And to take any elevations seriously, because this is a high risk population.

Well, audience you heard it right here on Circulation On The Run. I'm sure you've enjoyed this. I certainly have. Don't forget to tune in again next week.

SUPPLEMENTAL MATERIAL

0/1-hour triage algorithm for myocardial infarction in patients with renal dysfunction

Raphael Twerenbold et al.

Table of Contents

Supplemental Methods

Adjudication of the final diagnosis

AMI was defined and cTn levels interpreted as recommended in current guidelines.[1-4] In brief, AMI was diagnosed when there was evidence of myocardial necrosis with a significant rise and/or fall in a clinical setting consistent with myocardial ischemia. Patients with AMI were further subdivided into type 1 AMI (primary coronary events) and type 2 AMI (ischemia due to increased demand or decreased supply, for example tachyarrhythmia or hypertensive crisis).[2, 5]

The adjudication of final diagnoses was performed centrally in the core lab (University Hospital Basel) for all patients incorporating levels of hs-cTnT (see test characteristics above). More specifically, two independent cardiologists not directly involved in patient care reviewed all available medical records (including patient history, physical examination, results of laboratory testing including hs-cTnT levels, radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography, discharge summary) pertaining to the patient from the time of ED presentation to 90-day follow-up. Late samples were available for adjudication of final diagnosis in the vast majority of patients. In general, serial sampling was performed until at least 6h after presentation to the ED or onset of chest pain.[2] Distributions of latest study blood samples according to time since ED presentation and time since chest pain onset are listed in **supplemental Tables 2 and 3**. It is important to highlight that in many patients additional (hs)-cTn measurements at late time points using the local (hs)-cTn assays obtained as part of routine clinical care were also available for the adjudication. In situations of diagnostic disagreement, cases were reviewed

and adjudicated in conjunction with a third cardiologist. While discharge diagnoses often were correct and in agreement with the final adjudicated diagnosis, there were also cases where those diagnoses needed to be revised, most often because more information became available from medical testing during early follow-up, and more rarely, because the discharge diagnosis was not in agreement with the Universal Definition of AMI.

The 99th percentile (14ng/L) was used as cutoff for myocardial necrosis. Absolute cTn changes were used to determine significant changes based on the diagnostic superiority of absolute over relative changes.[6-11] Based on studies of the biological variation of cTn[12-14] as well as on data from previous chest pain cohort studies,[6, 15] a significant absolute change was defined as a rise or fall of at least 10ng/L within six hours, or, in an assumption of linearity, as an absolute change of 6ng/L within three hours. Predefined alternative diagnoses included “unstable angina” (UA), “Cardiac symptoms of origin other than coronary artery disease” and “non-cardiac chest pain”.

Clinical Care: The (hs)-cTn assays and cutoff levels used for local clinical care

Routine clinical care comprised five different cTn assays at the different hospitals and at the different recruitment periods. The cTn assays used clinically in most of the participating institutions changed during the study from a conventional cTn assay to the hs-cTnT assay. In order to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by the hs-cTnT assay, patients were adjudicated using the hs-cTnT values in all patients. In patients in whom clinically a conventional cTn assay was used, the conventional cTn values and the hs-cTnT values were available for the adjudication. In patients in whom clinically the hs-cTnT assay was used, only the hs-cTnT values were available for the adjudication.

The following conventional cTn assays were used:

For the Roche cTnT 4th generation assay, the 10% CV level is 0.035ug/l. The laboratories of the participating sites reported only two decimals; therefore 0.04ug/l was used as a cutoff for myocardial necrosis. In order to fulfil the criteria of a significant change (30% of 99th percentile or 10% CV level), a patient would e.g. need to have a level of <0.01ug/l at presentation and 0.04ug/l at 6h. A patient would also qualify if the first level is 0.02ug/l and the second 0.04ug/l. A patient would not fulfil the criteria if the first level is 0.03ug/l and the second is 0.04ug/l. If the first level is 0.04ug/l, the second level needs to be at least 0.06ug/l.

For the Abbott Axsym cTnI ADV, the 10% CV level is 0.16ug/l. A patient having 0.16ug/l at presentation would meet the criteria for significant change if the second was ≥0.21ug/l. A patient having <0.12ug/l at presentation (limit of detection) would qualify if the second is >0.16ug/l.

For the Beckmann Coulter Accu cTnI, the 10% CV level is 0.06ug/l. A patient having 0.06ug/l at presentation would qualify if the second is ≥0.08ug/l. A patient having 0.05 at presentation would qualify if the second is 0.07ug/l, but not 0.06ug/l. A patient having undetectable cTnI (cTnI<0.01ug/l) at presentation would qualify if the second is ≥0.06ug/l.

For the Siemens Dimension Vista s-cTnI, the 10% CV level is 40ng/L. The limit of detection is 15ng/L and the 99th percentile is 45ng/L. An absolute change of 20ng/L or more within 3-6h was considered significant.

For Elecsys hs-cTnT measured clinically, the same change criteria were applied as for hs-cTnT measured from the study blood samples.

Supplemental Tables

Supplemental Table 1: STARD Checklist for the Reporting of Studies of Diagnostic Accuracy

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1, 2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2-3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	5-6
	4	Study objectives and hypotheses	6
METHODS			
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
Participants	6	Eligibility criteria	7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	7
	9	Whether participants formed a consecutive, random or convenience series	7
Test methods	10a	Index test, in sufficient detail to allow replication	9-10
	10b	Reference standard, in sufficient detail to allow replication	8-9;Suppl. 2-4
	11	Rationale for choosing the reference standard (if alternatives exist)	8
	12a	Definition of and rationale for test positivity cutoffs or result categories of the index test, distinguishing pre-specified from exploratory	9-10
	12b	Definition of and rationale for test positivity cutoffs or result categories of the reference standard, distinguishing pre-specified from exploratory	Suppl. 2-4
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Suppl. 2-4
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Suppl. 2-4
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy	12-13
	15	How indeterminate index test or reference standard results were handled	7
	16	How missing data on the index test and reference standard were handled	7
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	n.a.
	18	Intended sample size and how it was determined	n.a.
RESULTS			
Participants	19	Flow of participants, using a diagram	Suppl. Fig. S2
	20	Baseline demographic and clinical characteristics of participants	Tab. 1
	21a	Distribution of severity of disease in those with the target condition	n.a.
	21b	Distribution of alternative diagnoses in those without the target condition	n.a.
	22	Time interval and any clinical interventions between index test and reference standard	n.a.
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	15-19
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	15-19
	25	Any adverse events from performing the index test or the reference standard	n.a.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	20-25
	27	Implications for practice, including the intended use and clinical role of the index test	20-25
OTHER INFORMATION			
	28	Registration number and name of registry	3
	29	Where the full study protocol can be accessed	3
	30	Sources of funding and other support; role of funders	26

Supplemental Table 2: Latest hs-cTnT value available x hours after presentation.

	All patients (n=3254)		Normal renal function (n=2767)		Renal dysfunction (n=487)	
	n	%	n	%	n	%
≥0h after presentation	3254	100%	2767	100%	487	100%
≥1h after presentation	3254	100%	2767	100%	487	100%
≥2h after presentation	2976	91%	2506	91%	470	97%
≥3h after presentation	2513	77%	2076	75%	437	90%
≥4h after presentation	2037	63%	1637	59%	400	82%
≥5h after presentation	1915	59%	1524	55%	391	80%
≥6h after presentation	1837	56%	1454	53%	383	79%

Supplemental Table 3: Latest hs-cTnT value available x hours after symptom onset.

	All patients (n=3254)		Normal renal function (n=2767)		Renal dysfunction (n=487)	
	n	%	n	%	n	%
≥0h after symptom onset	3254	100%	2767	100%	487	100%
≥1h after symptom onset	3254	100%	2767	100%	487	100%
≥2h after symptom onset	3250	100%	2763	100%	487	100%
≥3h after symptom onset	3226	99%	2741	99%	485	100%
≥4h after symptom onset	3152	97%	2672	97%	480	99%
≥5h after symptom onset	2995	92%	2518	91%	477	98%
≥6h after symptom onset	2884	89%	2379	86%	465	95%

Supplemental Table 4: Baseline Characteristics of Patients in Dataset B

	Normal Renal Function	Renal Dysunction*		Renal Dysfunction (n=445)		
				NSTEMI		
	n=2504	n=445	p-value†	Yes (n=143)	No (n=302)	p-value‡
Age – years	58 [47, 70]	79 [73, 84]	<0.001	80 [75, 86]	78 [72, 83]	0.003
Male gender	1755 (70)	259 (58)	<0.001	87 (61)	172 (57)	0.438
Risk factors						
Hypertension	1406 (56)	402 (90)	<0.001	132 (92)	270 (89)	0.333
Hypercholesterolemia	1138 (45)	311 (70)	<0.001	108 (76)	203 (67)	0.074
Diabetes mellitus	398 (16)	125 (28)	<0.001	49 (34)	76 (25)	0.046
Current smoking	699 (28)	9 (9)	<0.001	17 (12)	22 (7)	0.109
History of smoking	916 (37)	205 (46)	<0.001	67 (47)	138 (46)	0.819
History						
Coronary artery disease	737 (29)	256 (58)	<0.001	96 (67)	160 (53)	0.005
Previous myocardial infarction	518 (21)	184 (41)	<0.001	76 (53)	108 (36)	0.001
Previous revascularization	626 (25)	189 (42)	<0.001	69 (48)	120 (40)	0.090
Peripheral artery disease	100 (4)	57 (13)	<0.001	25 (17)	32 (11)	0.042
Previous stroke	113 (5)	55 (12)	<0.001	23 (16)	32 (11)	0.100
Vital Status						
Heart rate – bpm	76 [66, 88]	75 [65, 91]	0.785	81 [69, 97]	73 [63, 88]	0.002
Systolic blood pressure – mm Hg	142 [127, 158]	138 [121, 156]	0.001	137 [124, 157]	139 [121, 156]	0.983
Diastolic blood pressure – mm Hg	82 [73, 92]	73 [64, 84]	<0.001	73 [64, 83]	73 [64, 84]	0.831
Body-mass index – kg/m^2	26 [24, 30]	27 [24, 30]	0.230	26 [23, 28]	27 [25, 31]	<0.001
Electrocardiographic findings						
Left bundle branch block	71 (3)	45 (19)	<0.001	18 (13)	27 (9)	0.233
ST-segment depression	174 (7)	66 (15)	<0.001	36 (25)	30 (10)	<0.001
T-wave inversion	260 (10)	78 (18)	<0.001	37 (26)	41 (14)	0.001
Laboratory measurements						
Serum creatinine – µmol/l	73 [63, 83]	118 [100, 139]	<0.001	123 [105, 151]	116 [97, 134]	0.003
Estimated GFR – $ml/min/1.73m^2$	93 [81, 105]	48 [37, 55]	<0.001	45 [34, 52]	49 [40, 55]	<0.001
Early presenters (≤2 h after CPO)	92 (21)	650 (26)	0.018	32 (22)	60 (20)	0.541

*Categorical variables are presented as numbers (%), continuous variables are presented as medians [quartile 1, quartile 3]. CPO = chest pain onset; GFR = glomerular filtration rate; NSTEMI = Non-ST-Segment-Elevation Myocardial Infarction . Continuous variables were compared with the Mann-Whitney-U test, and categorical variables using the Pearson χ2 test or Fisher's exact test, as appropriate. *Renal dysfunction was diagnosed if the estimated GFR was <60mL/min/1.73m^2 using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula based on plasma creatinine levels obtained at presentation to the ED, age, sex and ethnicity. † for comparisons between patients with normal renal function and renal dysfunction. ‡ for comparisons between patients with and without acute myocardial infarction in the subset of patients with renal dysfunction.*

Supplemental Table 5: Baseline Characteristics of Patients in Dataset A and Dataset B

	Dataset A	Dataset B		Renal Dysfunction*		
				Dataset A	Dataset B	
	n=3254	n=2949	p-value†	n=487	n=445	p-value‡
Age – years	61 [49, 74]	62 [49, 74]	0.946	79 [73, 84]	79 [73, 84]	0.919
Male gender	2208 (68)	2014 (68)	0.711	284 (58)	259 (58)	0.972
Risk factors						
Hypertension	1993 (61)	1808 (61)	0.961	347 (71)	402 (90)	0.921
Hypercholesterolemia	1605 (49)	1449 (49)	0.882	347 (71)	311 (70)	0.648
Diabetes mellitus	570 (18)	523 (18)	0.822	136 (28)	125 (28)	0.956
Current smoking	814 (29)	738 (25)	0.993	44 (9)	9 (9)	0.885
History of smoking	1224 (38)	1121 (38)	0.747	223 (46)	205 (46)	0.932
History						
Coronary artery disease	1091 (34)	993 (34)	0.904	280 (57)	256 (58)	0.992
Previous myocardial infarction	780 (24)	702 (24)	0.878	204 (42)	184 (41)	0.867
Previous revascularization	904 (28)	815 (28)	0.899	209 (43)	189 (42)	0.891
Peripheral artery disease	172 (5)	157 (5)	0.947	62 (13)	57 (13)	0.972
Previous stroke	181 (6)	168 (6)	0.818	58 (12)	55 (12)	0.834
Vital Status						
Heart rate – bpm	76 [66, 89]	76 [66, 89]	0.940	75 [64, 91]	75 [65, 91]	0.806
Systolic blood pressure – mm Hg	141 [126, 158]	141 [126, 157]	0.874	138 [121, 156]	138 [121, 156]	0.960
Diastolic blood pressure – mm Hg	81 [71, 91]	81 [71, 91]	0.821	73 [64, 84]	73 [64, 84]	0.955
Body-mass index – kg/m^2	26 [24, 30]	27 [24, 30]	0.672	27 [24, 30]	27 [24, 30]	0.790
Electrocardiographic findings						
Left bundle branch block	124 (4)	116 (4)	0.802	48 (10)	45 (19)	0.896
ST-segment depression	166 (8)	140 (8)	0.959	74 (15)	66 (15)	0.877
T-wave inversion	372 (8)	338 (11)	0.971	84 (17)	78 (18)	0.910
Laboratory measurements						
Serum creatinine – µmol/l	76 [65, 89]	76 [65, 90]	0.943	118 [101, 140]	118 [100, 139]	0.841
Estimated GFR – $ml/min/1.73m^2$	89 [72, 102]	89 [72, 102]	0.779	48 [37, 55]	48 [37, 55]	0.940
Early presenters (≤2h after CPO)	828 (25)	742 (25)	0.797	97 (20)	92 (21)	0.774

*Categorical variables are presented as numbers (%), continuous variables are presented as medians [quartile 1, quartile 3]. CPO = chest pain onset; GFR = glomerular filtration rate. Continuous variables were compared with the Mann-Whitney-U test, and categorical variables using the Pearson χ2 test or Fisher's exact test, as appropriate. *Renal dysfunction was diagnosed if the estimated GFR was <60mL/min/1.73m^2 using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula based on plasma creatinine levels obtained at presentation to the ED, age, sex and ethnicity. † for comparisons between patients in Dataset A and Dataset B. ‡ for comparisons between patients with renal dysfunction in Dataset A and B.*

Supplemental Table 6: Distribution of the adjudicated final diagnoses.

	All patients n=3254	**Normal Renal Function** n=2767	**Renal Dysfunction** n=487	**p-value†**
Non-ST-Segment-Elevation Myocardial Infarction	515 (16)	364 (13)	151 (31)	<0.001
- Type 1	446 (14)	329 (12)	117 (24)	<0.001
- Type 2	68 (2)	35 (1)	33 (7)	<0.001
Unstable Angina	317 (10)	253 (9)	64 (13)	0.006
Cardiac cause, but not CAD*	491 (15)	396 (14)	95 (20)	0.001
Non-cardiac cause	1797 (55)	1634 (59)	163 (33)	0.001
Unknown	134 (4)	120 (4)	14 (3)	0.134

*CAD = coronary artery disease. * e.g. tachyarrhythmia, Tako-Tsubo cardiomyopathy, heart failure or myocarditis. † X^2-test for comparison of proportions in patients with normal renal function and renal dysfunction.*

Supplemental Table 7: Patients with an adjudicated diagnosis of Non-ST-Segment-Elevation Myocardial Infarction missed by the 0/1h-algorithm using high-sensitivity cardiac troponin T (n=3 of 3254), none of them with renal dysfunction.

Patient Number	Renal dysfunction	eGFR , mL/min/1.73m^2	Age	Sex	Time from chest pain onset to presentation, h	Time from chest pain peak to presentation, h	History of CAD	hs-cTnT, ng/L				hs-cTnI, ng/L				Ischemic ECG	Clinical discharge diagnosis	PCI performed	CABG performed
								0h	1h	2h	3-12h	0h	1h	2h	3-12h				
#1	no	71	74	female	1	1	no	10	12	17	17*	3.1	7.3	9.5	10.8*	no	unstable Angina	yes	no
#2	no	89	67	female	1	1	no	6	7	12	12*	4	8	18*		no	NSTEMI	yes	no
#3	no	64	86	female	17	3	yes	8*	7	7	7	27	24	27	29*	no	NSTEMI	no	no

*CAD = coronary artery disease; CABG = coronary artery bypass grafting; ECG = electrocardiography; eGFR=estimated glomerular filtration rate using CKD-EPI formula; hs-cTn = high-sensitivity cardiac troponin; PCI = percutaneous coronary intervention. * indicates peak level during serial sampling.*

Supplemental Table 8: Patients with an adjudicated diagnosis of Non-ST-Segment-Elevation Myocardial Infarction missed by the 0/1h-algorithm using high-sensitivity cardiac troponin I (n=7 of 2949), two of them with renal dysfunction.

Patient Number	Renal dysfunction	eGFR , mL/min/1.73m^2	Age	Sex	Time from chest pain onset to presentation, h	Time from chest pain peak to presentation, h	History of CAD	hs-cTnT, ng/L (peak value underlined)				hs-cTnI, ng/L (peak value underlined)				Ischemic ECG	Clinical discharge diagnosis	PCI performed	CABG performed
								0h	1h	2h	3-12h	0h	1h	2h	3-12h				
#1	yes	56	75	male	5	4	yes	39*	35			4.5	5.3*			no	cardiac arrhythmia	no	no
#2	yes	31	93	female	9	9	yes	41*	38		34	3.6*	2.4			no	unknown chest pain	no	no
#3	no	69	77	male	5	4	no	55*	53		45	4.7	4.8		5.1*	no	unknown chest pain	no	no
#4	no	95	73	male	4	4	yes	33*	32	28		3.4	3.9*			no	unknown chest pain	no	no
#5	no	72	75	male	1	1	yes	6	11	15*		2.9	4.8	8.8*		no	unstable angina	no	no
#6	no	104	52	male	4	4	no	43*	37	35	28	2.8*	2.8	2.5		no	unknown chest pain	no	no
#7	no	69	79	female	1	1	yes	18	19	22	24*	3.9	5.8	7.0*		yes	cardiac arrhythmia	no	no

*CAD = coronary artery disease; CABG = coronary artery bypass grafting; ECG = electrocardiography; eGFR=estimated glomerular filtration rate using CKD-EPI formula; hs-cTn = high-sensitivity cardiac troponin; PCI = percutaneous coronary intervention. * indicates peak hs-cTn level during serial sampling.*

Supplemental Table 9: Performance of the European Society of Cardiology 0/1h-algorithm in patients with renal dysfunction and normal renal function presenting within 2 hours after chest pain onset to the emergency department.

Using high-sensitivity cardiac troponin T

	Renal dysfunction - n=97	Normal renal function - n=731	p-value*
Prevalence of NSTEMI	36	13	<0.001
Sensitivity of rule-out	100.0 (90.0-100.0)	98.0 (92.8-99.8)	1.0
NPV of rule-out	100.0 (n.a.)	99.6 (98.5-99.9)	1.0
Specificity of rule-in	90.3 (80.1-96.4)	95.7 (93.9-97.2)	0.056
PPV of rule-in	82.7 (69.0-91.3)	73.5 (65.4-80.3)	0.267
Proportion ruled-out	19.6 (11.6-28.4)	70.3 (66.8-73.6)	<0.001
- based on 0h-sample only	-	-	-
- based on 0h/1h-samples	19.6 (11.6-28.4)	70.3 (66.8-73.6)	<0.001
Proportion ruled-in	36.1 (26.6-45.2)	14.0 (11.5-16.5)	<0.001
- based on 0h-sample only	23.7 (15.2-32.7)	4.5 (3.1-6.1)	<0.001
- based on 1h-change	12.4 (6.2-19.2)	9.4 (7.5-11.7)	0.361
Overall Efficacy	55.7 (46.0-64.9)	84.3 (81.4-86.8)	<0.001
Prevalence of NSTEMI in the observational group	14 (4-26)	18 (11-25)	0.522

Using high-sensitivity cardiac troponin I

	Renal dysfunction - n=92	Normal renal function - n=650	p-value*
Prevalence of NSTEMI	35	14	<0.001
Sensitivity of rule-out	100.0 (89.1-100.0)	97.7 (92.0-99.7)	1.0
NPV of rule-out	100.0 (n.a.)	99.5 (98.1-99.9)	1.0
Specificity of rule-in	88.3 (77.4-95.2)	92.5 (90.0-94.6)	0.252
PPV of rule-in	76.7 (61.3-87.2)	63.8 (56.5-70.5)	0.185
Proportion ruled-out	23.9 (15.4-32.6)	61.4 (57.6-65.1)	<0.001
- based on 0h-sample only	-	-	-
- based on 0/1h-samples	23.9 (15.4-32.6)	61.4 (57.6-65.1)	<0.001
Proportion ruled-in	32.6 (23.4-43.3)	17.8 (15.0-20.7)	0.001
- based on 0h-sample only	17.4 (9.6-25.5)	8.8 (6.7-10.9)	0.009
- based on 1h-change	15.2 (8.1-23.4)	9.1 (6.9-11.3)	0.064
Overall Efficacy	55.4 (45.3-65.9)	82.6 (79.6-85.5)	<0.001
Prevalence of NSTEMI in the observational group	23 (10-36)	9 (4-14)	0.020

*Numbers represent percentage (95% confidence interval). * performances measures in patients with renal dysfunction and normal renal function were compared using χ2 or Fisher's exact test. n.a.= not applicable; NPV = negative predictive value; NSTEMI = Non-ST-Segment-Elevation Myocardial Infarction, PPV = positive predictive value.*

Supplemental Table 10: Performance of the European Society of Cardiology 0/1h-algorithm in patients with renal dysfunction and presence or absence of pre-existing kidney disease.

Using high-sensitivity cardiac troponin T

	Pre-existing kidney disease		p-value*
	present - n=276	absent - n=211	
Prevalence of NSTEMI	37	24	0.002
Sensitivity of rule-out	100.0 (96.4-100.0)	100.0 (92.9-100.0)	1.0
NPV of rule-out	100.0 (n.a.)	100.0 (n.a.)	1.0
Specificity of rule-in	88.0 (82.2-92.4)	89.4 (83.6-93.7)	0.677
PPV of rule-in	79.8 (72.4-85.6)	70.7 (60.2-79.4)	0.136
Proportion ruled-out	10.9 (7.3-14.9)	27.5 (21.5-33.6)	<0.001
- based on 0h-sample only	0.4 (0.0-1.2)	2.8 (0.9-5.2)	0.023
- based on 0h/1h-samples	10.5 (6.9-14.4)	24.6 (19.2-30.8)	<0.001
Proportion ruled-in	37.7 (32.0-43.0)	27.5 (21.7-33.9)	0.018
- based on 0h-sample only	29.3 (23.8-34.9)	21.3 (15.9-27.4)	0.364
- based on 1h-change	8.3 (5.1-11.8)	6.2 (3.1-9.9)	0.160
Overall Efficacy	48.6 (42.4-54.1)	55.0 (47.9-61.6)	0.160
Prevalence of NSTEMI in the observational group	13 (7-19)	10 (4-16)	0.447

Using high-sensitivity cardiac troponin I

	Pre-existing kidney disease		p-value*
	present - n=251	absent - n=194	
Prevalence of NSTEMI	38	24	0.002
Sensitivity of rule-out	100.0 (96.2-100.0)	95.7 (85.5-99.5)	0.106
NPV of rule-out	100.0 (n.a.)	95.7 (84.7-98.9)	0.510
Specificity of rule-in	81.3 (74.3-87.1)	87.8 (81.3-92.6)	0.122
PPV of rule-in	72.4 (65.0-78.7)	67.9 (57.3-76.9)	0.549
Proportion ruled-out	12.7 (8.8-17.2)	23.7 (18.0-29.8)	0.003
- based on 0h-sample only	0.4 (0.0-1.3)	2.6 (0.5-5.1)	0.048
- based on 0h/1h-samples	12.4 (8.5-16.5)	21.1 (15.6-27.0l	0.013
Proportion ruled-in	41.8 (36.0-47.6)	28.9 (22.5-35.7)	0.005
- based on 0h-sample only	30.3 (25.1-36.3)	22.7 (16.8-28.8)	0.073
- based on 1h-change	11.6 (7.8-15.6)	6.2 (2.9-9.6)	0.052
Overall Efficacy	54.6 (48.2-60.8)	52.1 (44.8-58.9)	0.597
Prevalence of NSTEMI in the observational group	18 (11-24)	8 (3-14)	0.033

*Numbers represent percentage (95% confidence interval). * performances measures in patients with and without pre-existing kidney disease were compared using $\chi 2$ or Fisher's exact test. n.a.= not applicable; NPV = negative predictive value; NSTEMI = Non-ST-Segment-Elevation Myocardial Infarction, PPV = positive predictive value.*

Supplemental Table 11: Performance of the European Society of Cardiology 0/1h-algorithm in women and men with renal dysfunction.

Using high-sensitivity cardiac troponin T			
	Women - n=203	**Men - n=284**	**p-value***
Prevalence of NSTEMI	29	33	0.326
Sensitivity of rule-out	100.0 (93.8-100.0)	100.0 (96.1-100.0)	1.0
NPV of rule-out	100.0 (n.a.)	100.0 (n.a.)	1.0
Specificity of rule-in	91.0 (85.2-95.1)	86.9 (81.3-91.4)	0.238
PPV of rule-in	80.6 (71.1-87.5)	73.7 (65.6-80.4)	0.310
Proportion ruled-out	28.1 (22.1-34.2)	10.9 (7.4-14.9)	<0.001
- based on 0h-sample only	3.0 (0.9-5.7)	0.4 (0.0-1.2)	0.017
- based on 0h/1h-samples	25.1 (19.3-31.1)	10.6 (7.1-14.4)	<0.001
Proportion ruled-in	33.0 (26.9-39.9)	33.5 (27.7-38.6)	0.918
- based on 0h-sample only	22.2 (16.7-28.8)	28.5 (23.3-33.5)	0.114
- based on 1h-change	10.8 (6.8-15.7)	4.9 (2.7-7.4)	0.014
Overall Efficacy	61.1 (54.7-67.5)	44.4 (38.5-50.4)	<0.001
Prevalence of NSTEMI in the observational group	5 (0-10)	15 (9-21)	0.030
Using high-sensitivity cardiac troponin I			
	Women - n=186	**Men - n=259**	**p-value***
Prevalence of NSTEMI	30	34	0.438
Sensitivity of rule-out	98.2 (90.5-100.0)	98.9 (93.8-100.0)	1.0
NPV of rule-out	97.7 (85.9-99.7)	97.1 (82.1-99.6)	1.0
Specificity of rule-in	88.5 (75.9-94.8)	81.4 (74.8-86.9)	0.094
PPV of rule-in	76.6 (66.8-84.2)	67.0 (59.2-74.0)	0.193
Proportion ruled-out	23.7 (17.5-29.7)	13.1 (9.1-17.2)	0.004
- based on 0h-sample only	1.6 (0.0-3.6)	1.2 (0.0-2.6)	0.682
- based on 0h/1h-samples	22.0 (15.9-28.2)	12.0 (8.1-15.8)	0.004
Proportion ruled-in	34.4 (27.8-41.4)	37.5 (31.6-43.2)	0.510
- based on 0h-sample only	25.8 (19.9-32.2)	27.8 (21.8-33.2)	0.640
- based on 1h-change	8.6 (5.0-12.8)	9.7 (5.9-13.6)	0.706
Overall Efficacy	58.1 (50.6-65.0)	50.2 (43.9-56.0)	0.101
Prevalence of NSTEMI in the observational group	8 (2-15)	16 (11-23)	0.075

*Numbers represent percentage (95% confidence interval). *performances measures in male and femal patients were compared using $\chi 2$ or Fisher's exact test. n.a.= not applicable; NPV = negative predictive value; NSTEMI = Non-ST-Segment-Elevation Myocardial Infarction, PPV = positive predictive value.*

Supplemental Table 12: Performance of the European Society of Cardiology 0/1h-algorithm in patients with renal dysfunction and normal renal function after exclusion of patients that were part of the original derivation cohorts.

Using high-sensitivity cardiac troponin T

	Renal dysfunction - n=418	Normal renal function - n=2428	p-value*
Prevalence of NSTEMI	31	13	<0.001
Sensitivity of rule-out	100.0 (97.2-100.0)	99.0 (97.2-99.8)	0.559
NPV of rule-out	100.0 (n.a.)	99.8 (99.5-99.9)	1.0
Specificity of rule-in	90.3 (86.3-93.4)	96.6 (95.8-97.4)	<0.001
PPV of rule-in	78.6 (71.9-84.1)	77.2 (72.7-81.1)	0.738
Proportion ruled-out	18.7 (15.2-22.4)	68.5 (66.7-70.2)	<0.001
- based on 0h-sample only	1.4 (0.5-2.7)	18.0 (16.4-19.5)	<0.001
- based on 0h/1h-samples	17.2 (1.9-20.9)	50.5 (48.7-52.3)	<0.001
Proportion ruled-in	31.3 (26.9-35.7)	12.8 (11.5-14.2)	<0.001
- based on 0h-sample only	23.9 (19.8-28.0)	7.7 (6.7-8.8)	<0.001
- based on 1h-change	7.4 (5.1-10.1)	5.1 (4.2-6.0)	0.050
Overall Efficacy	50.0 (45-55.0)	81.3 (79.8-82.9)	<0.001
Prevalence of NSTEMI in the observational group	13 (8-18)	16 (13-19)	0.359

Using high-sensitivity cardiac troponin I

	Renal dysfunction - n=313	Normal renal function - n=1740	p-value*
Prevalence of NSTEMI	28	13	<0.001
Sensitivity of rule-out	100.0 (95.9-100.0)	99.1 (96.8-99.9)	1.0
NPV of rule-out	100.0 (n.a.)	99.8 (99.2-100.0)	1.0
Specificity of rule-in	84.0 (78.5-88.5)	90.5 (88.9-91.9)	0.003
PPV of rule-in	65.7 (58.2-72.5)	57.9 (53.9-61.8)	0.153
Proportion ruled-out	17.6 (13.5-21.8)	55.6 (54.4-59.0)	<0.001
- based on 0h-sample only	1.3 (0.3-2.5)	11.3 (9.7-12.8)	<0.001
- based on 0h/1h-samples	16.3 (12.2-20.5)	45.3 (43.2-47.6)	<0.001
Proportion ruled-in	33.5 (28.4-38.7)	19.7 (17.7-21.5)	<0.001
- based on 0h-sample only	24.3 (19.8-29.2)	13.8 (12.2-15.4)	<0.001
- based on 1h-change	9.3 (6.0-12.5)	5.9 (4.8-7.0)	0.023
Overall Efficacy	52.1 (46.8-57.4)	76.2 (74.3-78.2)	<0.001
Prevalence of NSTEMI in the observational group	12 (7-18)	6 (4-8)	0.013

*408 patients of dataset A were part of the original derivation cohort of the hs-cTnT 0/1h-algorithm and 896 patients of dataset B were part of the original derivation cohort of the hs-cTnI 0/1h-algorithm. Numbers represent percentage (95% confidence interval). * performances measures in patients with renal dysfunction and normal renal function were compared using $\chi 2$ or Fisher's exact test. n.a. = not applicable; NPV = negative predictive value; NSTEMI = Non-ST-Segment-Elevation Myocardial Infarction, PPV = positive predictive value.*

Supplemental Table 13: Diagnostic performance of multiple cutoff criteria combinations using high-sensitivity cardiac troponin T (based on 0-hour sample concentration and 1-hour change) for rapid rule-out and rule-in of Non-ST-Segment-Elevation Myocardial Infarction in patients with renal dysfunction.

	Criteria					**Diagnostic Performance**			
	Direct Rule-out based on 0h-sample	**OR**	**Rule-out based on 0h- and 1h- sample**			**Rule-out Sensitivity (95% CI)**	**Rule-out NPV (95% CI)**	**Proportion Rule-out (95% CI)**	**Proportion direct Rule-out based on 0h-sample only (95% CI)**
	0h hs-cTnT		**0h hs-cTnT**	**AND**	**1h-change hs-cTnT**				
Rule-out strategy	**<5 ng/L**	OR	**<12 ng/L**	AND	**<3 ng/L**	100.0 (97.6-100)	100.0 (n.a.)	18.1 (14.6-21.6)	1.4 (0.4-2.6)
					<4 ng/L	100.0 (97.6-100)	100.0 (n.a.)	18.1 (14.6-21.6)	1.4 (0.4-2.6)
			<14 ng/L		<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	22.6 (18.8-26.7)	1.4 (0.4-2.6)
					<4 ng/L	99.3 (96.4-100)	99.1 (94.0-99.9)	23.0 (19.2-27.1)	1.4 (0.4-2.6)
			<16 ng/L		<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	29.0 (25.1-33.1)	1.4 (0.4-2.6)
					<4 ng/L	99.3 (96.4-100)	99.3 (95.3-99.9)	29.4 (25.4-33.5)	1.4 (0.4-2.6)
			<18 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.8 (95.3-99.7)	33.5 (29.1-37.8)	1.4 (0.4-2.6)
					<4 ng/L	97.4 (93.4-99.3)	97.6 (93.9-99.1)	34.1 (29.7-38.4)	1.4 (0.4-2.6)
			<20 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.9 (95.7-99.7)	37.0 (32.7-41.3)	1.4 (0.4-2.6)
					<4 ng/L	96.7 (92.4-98.9)	97.3 (93.8-98.9)	38.0 (33.7-42.5)	1.4 (0.4-2.6)
	<6 ng/L	OR	<12 ng/L	AND	<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	18.1 (14.6-21.6)	1.6 (0.6-2.9)
					<4 ng/L	100.0 (97.6-100)	100.0 (n.a.)	18.1 (14.6-21.6)	1.6 (0.6-2.9)
			<14 ng/L		*<3 ng/L*	100.0 (97.6-100)	100.0 (n.a.)	22.6 (18.8-26.7)	1.6 (0.6-2.9)
					<4 ng/L	99.3 (96.4-100)	99.1 (94.0-99.9)	23.0 (19.2-27.1)	1.6 (0.6-2.9)
			<16 ng/L		<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	29.0 (25.1-33.1)	1.6 (0.6-2.9)
					<4 ng/L	99.3 (96.4-100)	99.3 (95.3-99.9)	29.4 (25.4-33.5)	1.6 (0.6-2.9)
			<18 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.8 (95.3-99.7)	33.5 (29.1-37.8)	1.6 (0.6-2.9)
					<4 ng/L	97.4 (93.4-99.3)	97.6 (93.9-99.1)	34.1 (29.7-38.4)	1.6 (0.6-2.9)
			<20 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.9 (95.7-99.7)	37.0 (32.7-41.3)	1.6 (0.6-2.9)
					<4 ng/L	96.7 (92.4-98.9)	97.3 (93.8-98.9)	38.0 (33.7-42.5)	1.6 (0.6-2.9)
	<8 ng/L	OR	<12 ng/L	AND	<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	18.1 (14.6-21.6)	4.9 (3.1-7.0)
					<4 ng/L	100.0 (97.6-100)	100.0 (n.a.)	18.1 (14.6-21.6)	4.9 (3.1-7.0)
			<14 ng/L		<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	22.6 (18.8-26.7)	4.9 (3.1-7.0)
					<4 ng/L	99.3 (96.4-100)	99.1 (94.0-99.9)	23.0 (19.2-27.1)	4.9 (3.1-7.0)
			<16 ng/L		<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	29.0 (25.1-33.1)	4.9 (3.1-7.0)
					<4 ng/L	99.3 (96.4-100)	99.3 (95.3-99.9)	29.4 (25.4-33.5)	4.9 (3.1-7.0)
			<18 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.8 (95.3-99.7)	33.5 (29.1-37.8)	4.9 (3.1-7.0)
					<4 ng/L	97.4 (93.4-99.3)	97.6 (93.9-99.1)	34.1 (29.7-38.4)	4.9 (3.1-7.0)
			<20 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.9 (95.7-99.7)	37.0 (32.7-41.3)	4.9 (3.1-7.0)
					<4 ng/L	96.7 (92.4-98.9)	97.3 (93.8-98.9)	38.0 (33.7-42.5)	4.9 (3.1-7.0)

Supplemental Table 13 (continued): Diagnostic performance of multiple cutoff criteria combinations using high-sensitivity cardiac troponin T (based on 0-hour sample concentration and 1-hour change) for rapid rule-out and rule-in of Non-ST-Segment-Elevation Myocardial Infarction in patients with renal dysfunction.

	Criteria					Diagnostic Performance			
	Direct Rule-out based on 0h-sample	OR	Rule-out based on 0h- and 1h- sample			Rule-out Sensitivity (95% CI)	Rule-out NPV (95% CI)	Proportion Rule-out (95% CI)	Proportion direct Rule-out based on 0h-sample only (95% CI)
	0h hs-cTnT		0h hs-cTnT	AND	1h-change hs-cTnT				
Rule-out strategy	<10 ng/L	OR	<12 ng/L	AND	<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	18.1 (14.6-21.6)	9.0 (6.5-11.6)
					<4 ng/L	100.0 (97.6-100)	100.0 (n.a.)	18.1 (14.6-21.6)	9.0 (6.5-11.6)
			<14 ng/L		<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	22.6 (18.8-26.7)	9.0 (6.5-11.6)
					<4 ng/L	99.3 (96.4-100)	99.1 (94.0-99.9)	23.0 (19.2-27.1)	9.0 (6.5-11.6)
			<16 ng/L		<3 ng/L	100.0 (97.6-100)	100 (n.a.)	29.0 (25.1-33.1)	9.0 (6.5-11.6)
					<4 ng/L	99.3 (96.4-100)	99.3 (95.3-99.9)	29.4 (25.4-33.5)	9.0 (6.5-11.6)
			<18 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.8 (95.3-99.7)	33.5 (29.1-37.8)	9.0 (6.5-11.6)
					<4 ng/L	97.4 (93.4-99.3)	97.6 (93.9-99.1)	34.1 (29.7-38.4)	9.0 (6.5-11.6)
			<20 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.9 (95.7-99.7)	37.0 (32.7-41.3)	9.0 (6.5-11.6)
					<4 ng/L	96.7 (92.4-98.9)	97.3 (93.8-98.9)	38.0 (33.7-42.5)	9.0 (6.5-11.6)
	<12 ng/L	OR	<14 ng/L	AND	<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	22.6 (18.8-26.7)	12.3 (9.5-15.3)
					<4 ng/L	99.3 (96.4-100)	99.1 (94.0-99.9)	23.0 (19.2-27.1)	12.3 (9.5-15.3)
			<16 ng/L		<3 ng/L	100.0 (97.6-100)	100.0 (n.a.)	29.0 (25.1-33.1)	12.3 (9.5-15.3)
					<4 ng/L	99.3 (96.4-100)	99.3 (95.3-99.9)	29.4 (25.4-33.5)	12.3 (9.5-15.3)
			<18 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.8 (95.3-99.7)	33.5 (29.1-37.8)	12.3 (9.5-15.3)
					<4 ng/L	97.4 (93.4-99.3)	97.6 (93.9-99.1)	34.1 (29.7-38.4)	12.3 (9.5-15.3)
			<20 ng/L		<3 ng/L	98.7 (95.3-99.8)	98.9 (95.7-99.7)	37.0 (32.7-41.3)	12.3 (9.5-15.3)
					<4 ng/L	96.7 (92.4-98.9)	97.3 (93.8-98.9)	38.0 (33.7-42.5)	12.3 (12.3-18.8)
	<14 ng/L	OR	<16 ng/L	AND	<3 ng/L	99.3 (96.4-100)	99.3 (95.3-99.9)	29.2 (25.3-33.2)	15.4 (12.3-18.8)
					<4 ng/L	99.3 (96.4-100)	99.3 (95.3-99.9)	29.4 (25.4-33.5)	15.4 (12.3-18.8)
			<18 ng/L		<3 ng/L	98.0 (94.3-99.6)	98.2 (94.6-99.4)	33.7 (29.4-38.2)	15.4 (12.3-18.8)
					<4 ng/L	97.4 (93.4-99.3)	97.6 (93.9-99.1)	34.1 (29.7-38.4)	15.4 (12.3-18.8)
			<20 ng/L		<3 ng/L	98.0 (94.3-99.6)	98.3 (95.1-99.5)	37.2 (32.9-41.5)	15.4 (12.3-18.8)
					<4 ng/L	96.7 (92.4-98.9)	97.3 (93.8-98.9)	38.0 (33.7-42.5)	15.4 (12.3-18.8)

Supplemental Table 13 (continued): Diagnostic performance of multiple cutoff criteria combinations using high-sensitivity cardiac troponin T (based on 0-hour sample concentration and 1-hour change) for rapid rule-out and rule-in of Non-ST-Segment-Elevation Myocardial Infarction in patients with renal dysfunction.

	Criteria			Diagnostic Performance			
	Direct Rule-in based on 0h-sample	OR	Rule-in based on 1h-change	Rule-in Specificity (95% CI)	Rule-in PPV (95% CI)	Proportion Rule-in (95% CI)	Proportion direct Rule-in based on 0h-sample only (95% CI)
	0h hs-cTnT		1h-change hs-cTnT				
Rule-in strategy	**≥52 ng/L**	OR	**≥5 ng/L**	88.7 (84.8-91.9)	76.5 (70.6-81.6)	33.3 (29.3-37.5)	25.9 (22.4-29.7)
			≥6 ng/L	89.9 (86.2-92.9)	78.2 (82.1-83.3)	32.0 (28.3-36.3)	25.9 (22.4-29.7)
			≥7 ng/L	89.9 (86.2-92.9)	77.6 (71.4-82.8)	31.2 (27.4-35.4)	25.9 (22.4-29.7)
			≥8 ng/L	89.9 (86.2-92.9)	77.3 (71.0-82.6)	30.8 (26.8-34.9)	25.9 (22.4-29.7)
			≥9 ng/L	89.9 (86.2-92.9)	77.0 (70.7-82.4)	30.4 (26.5-34.6)	25.9 (22.4-29.7)
	≥60 ng/L	OR	≥5 ng/L	90.5 (86.8-93.4)	78.2 (71.9-83.5)	30.2 (26.2-34.3)	19.7 (16.3-23.2)
			≥6 ng/L	92.0 (88.5-94.6)	80.6 (74.1-85.8)	28.5 (24.6-32.5)	19.7 (16.3-23.2)
			≥7 ng/L	92.0 (88.5-94.6)	80.0 (73.3-85.3)	27.7 (24.0-31.6)	19.7 (16.3-23.2)
			≥8 ng/L	92.6 (89.2-95.1)	80.8 (74.0-86.1)	26.7 (22.7-30.6)	19.7 (16.3-23.2)
			≥9 ng/L	92.6 (89.2-95.1)	80.2 (73.2-85.7)	25.9 (22.0-29.7)	19.7 (16.3-23.2)
	≥80 ng/L	OR	*≥5 ng/L*	92.6 (89.2-95.1)	81.5 (74.9-86.7)	27.7 (23.7-31.7)	15.2 (11.9-18.4)
			≥6 ng/L	94.4 (91.3-96.6)	84.9 (78.2-89.8)	25.9 (22.1-29.8)	15.2 (11.9-18.4)
			≥7 ng/L	94.4 (91.3-96.6)	84.3 (77.4-89.4)	24.8 (21.1-28.7)	15.2 (11.9-18.4)
			≥8 ng/L	94.9 (92.0-97.0)	85.2 (78.1-90.3)	23.6 (19.8-27.3)	15.2 (11.9-18.4)
			≥9 ng/L	94.9 (92.0-97.0)	84.7 (77.4-89.9)	22.8 (19.2-26.6)	15.2 (11.9-18.4)
	≥100 ng/L	OR	≥5 ng/L	93.8 (90.6-96.1)	83.7 (77.1-88.7)	26.5 (22.7-30.5)	11.3 (8.6-14.2)
			≥6 ng/L	95.5 (92.7-97.5)	87.4 (80.7-92.0)	24.4 (20.7-28.4)	11.3 (8.6-14.2)
			≥7 ng/L	95.5 (92.7-97.5)	86.7 (79.7-91.6)	23.2 (19.5-26.9)	11.3 (8.6-14.2)
			≥8 ng/L	96.1 (93.5-97.9)	87.6 (80.4-92.5)	21.6 (17.8-25.3)	11.3 (8.6-14.2)
			≥9 ng/L	96.1 (93.5-97.9)	87.0 (79.4-92.1)	20.5 (16.9-23.9)	11.3 (8.6-14.2)
	≥120 ng/L	OR	≥5 ng/L	94.1 (91.0-96.3)	87.5 (84.6-90.0)	25.9 (22.1-29.8)	9.0 (6.6-11.6)
			≥6 ng/L	96.1 (93.5-97.9)	88.7 (82.0-93.1)	23.6 (19.8-27.5)	9.0 (6.6-11.6)
			≥7 ng/L	96.1 (93.5-97.9)	88.1 (81.0-92.7)	22.4 (18.7-26.1)	9.0 (6.6-11.6)
			≥8 ng/L	97.0 (94.6-98.6)	89.9 (82.7-94.3)	20.3 (16.7-23.9)	9.0 (6.6-11.6)
			≥9 ng/L	97.0 (94.6-98.6)	89.4 (81.8-94.0)	19.3 (15.8-22.7)	9.0 (6.6-11.6)

n.a. = not applicable. Bold printed cutoff criteria indicate the official ESC cutoff criteria combination for rule-out and rule-in; italic printed cutoff criteria indicate the alternative, modified cutoff criteria combination for patients with renal dysfunction.

Supplemental Table 14: Diagnostic performance of multiple cutoff criteria combinations using high-sensitivity cardiac troponin I (based on 0-hour sample concentration and 1-hour change) for rapid rule-out and rule-in of Non-ST-Segment-Elevation Myocardial Infarction in patients with renal dysfunction.

	Criteria					Diagnostic Performance			
	Direct Rule-out based on 0h-sample	OR	Rule-out based on 0h- and 1h- sample			Rule-out Sensitivity (95% CI)	Rule-out NPV (95% CI)	Proportion Rule-out (95% CI)	Proportion direct Rule-out based on 0h-sample only (95% CI)
	0h hs-cTnI		0h hs-cTnI	AND	1h-change hs-cTnI				
Rule-out strategy	**<2 ng/L**	OR	**<5 ng/L**	AND	**<2 ng/L**	98.6 (95.0-99.8)	97.4 (90.5-99.4)	17.5 (13.9-21.4)	1.3 (0.4-2.5)
					<3 ng/L	98.6 (95.0-99.8)	97.5 (90.8-99.4)	18.2 (14.5-22.1)	1.3 (0.4-2.5)
			<6 ng/L		<2 ng/L	98.6 (95.0-99.8)	97.9 (92.2-99.5)	21.8 (17.9-25.8)	1.3 (0.4-2.5)
					<3 ng/L	98.6 (95.0-99.8)	98.0 (92.5-99.5)	22.7 (18.8-26.7)	1.3 (0.4-2.5)
			<7 ng/L		<2 ng/L	97.2 (93.0-99.2)	96.4 (91.0-98.6)	25.2 (21.2-29.4)	1.3 (0.4-2.5)
					<3 ng/L	97.2 (93.0-99.2)	96.7 (91.6-98.7)	27.0 (22.6-31.3)	1.3 (0.4-2.5)
			<8 ng/L		<2 ng/L	96.5 (92.0-98.9)	96.0 (91.0-98.3)	28.3 (24.1-32.6)	1.3 (0.4-2.5)
					<3 ng/L	96.5 (92.0-98.9)	96.4 (91.8-98.5)	31.0 (26.4-35.2)	1.3 (0.4-2.5)
	<3 ng/L	OR	<5 ng/L	AND	<2 ng/L	98.6 (95.0-99.8)	97.4 (90.5-99.4)	17.5 (13.9-21.4)	3.4 (1.8-5.2)
					<3 ng/L	98.6 (95.0-99.8)	97.5 (90.8-99.4)	18.2 (14.5-22.1)	3.4 (1.8-5.2)
			<6 ng/L		<2 ng/L	98.6 (95.0-99.8)	97.9 (92.2-99.5)	21.8 (17.9-25.8)	3.4 (1.8-5.2)
					<3 ng/L	98.6 (95.0-99.8)	98.0 (92.5-99.5)	22.7 (18.8-26.7)	3.4 (1.8-5.2)
			<7 ng/L		<2 ng/L	97.2 (93.0-99.2)	96.4 (91.0-98.6)	25.2 (21.2-29.4)	3.4 (1.8-5.2)
					<3 ng/L	97.2 (93.0-99.2)	96.7 (91.6-98.7)	27.0 (22.6-31.3)	3.4 (1.8-5.2)
			<8 ng/L		<2 ng/L	96.5 (92.0-98.9)	96.0 (91.0-98.3)	28.3 (24.1-32.6)	3.4 (1.8-5.2)
					<3 ng/L	96.5 (92.0-98.9)	96.4 (91.8-98.5)	31.0 (26.4-35.2)	3.4 (1.8-5.2)
	<4 ng/L	OR	<5 ng/L	AND	<2 ng/L	98.6 (95.0-99.8)	97.5 (90.7-99.4)	18.0 (14.4-21.8)	7.6 (5.3-10.2)
					<3 ng/L	98.6 (95.0-99.8)	97.6 (90.9-99.4)	18.4 (14.7-22.2)	7.6 (5.3-10.2)
			<6 ng/L		*<2 ng/L*	98.6 (95.0-99.8)	98.0 (92.4-99.5)	22.2 (18.3-26.2)	7.6 (5.3-10.2)
					<3 ng/L	98.6 (95.0-99.8)	98.0 (92.6-99.5)	22.9 (19.0-26.9)	7.6 (5.3-10.2)
			<7 ng/L		<2 ng/L	97.2 (93.0-99.2)	96.5 (91.2-98.7)	25.6 (21.5-29.9)	7.6 (5.3-10.2)
					<3 ng/L	97.2 (93.0-99.2)	96.7 (91.7-98.7)	27.2 (22.8-31.5)	7.6 (5.3-10.2)
			<8 ng/L		<2 ng/L	96.4 (91.9-98.8)	96.1 (91.1-98.3)	28.8 (24.5-33.0)	7.6 (5.3-10.2)
					<3 ng/L	96.5 (92.0-98.9)	96.4 (91.8-98.5)	31.2 (26.7-35.3)	7.6 (5.3-10.2)
	<5 ng/L	OR	<6 ng/L	AND	<2 ng/L	97.9 (94.0-99.6)	97.0 (91.3-99.0)	22.7 (18.9-26.7)	11.5 (8.5-14.6)
					<3 ng/L	97.9 (94.0-99.6)	97.1 (91.5-99.0)	23.1 (19.1-27.1)	11.5 (8.5-14.6)
			<7 ng/L		<2 ng/L	96.5 (92.0-98.9)	95.7 (90.3-98.2)	26.1 (22.0-30.2)	11.5 (8.5-14.6)
					<3 ng/L	96.5 (92.0-98.9)	95.9 (90.7-98.3)	27.4 (23.1-31.7)	11.5 (8.5-14.6)
			<8 ng/L		<2 ng/L	95.8 (91.1-98.4)	95.4 (90.3-97.9)	29.2 (24.9-33.5)	11.5 (8.5-14.6)
					<3 ng/L	95.8 (91.1-98.4)	95.7 (91.0-98.0)	31.5 (26.9-35.7)	11.5 (8.5-14.6)
	<6 ng/L	OR	<7 ng/L		<2 ng/L	96.5 (92.0-98.9)	95.7 (90.3-98.2)	26.3 (22.3-30.5)	14.2 (11-17.4)
					<3 ng/L	96.5 (92.0-98.9)	95.9 (90.8-98.3)	27.6 (23.3-32.0)	14.2 (11-17.4)
			<8 ng/L		<2 ng/L	95.8 (91.1-98.4)	95.4 (90.4-97.9)	29.4 (25.1-33.8)	14.2 (11-17.4)
					<3 ng/L	95.8 (91.1-98.4)	95.7 (91.1-98.0)	31.7 (27.2-35.9)	14.2 (11-17.4)

Supplemental Table 14 (continued): Diagnostic performance of multiple cutoff criteria combinations using high-sensitivity cardiac troponin I (based on 0-hour sample concentration and 1-hour change) for rapid rule-out and rule-in of Non-ST-Segment-Elevation Myocardial Infarction in patients with renal dysfunction.

	Criteria			Diagnostic Performance			
	Direct Rule-in based on 0h-sample 0h hs-cTnI	OR	Rule-in based on 1h-change 1h-change hs-cTnI	Rule-in Specificity (95% CI)	Rule-in PPV (95% CI)	Proportion Rule-in (95% CI)	Proportion direct Rule-in based on 0h-sample only (95% CI)
Rule-in strategy	**≥52 ng/L**	OR	**≥6 ng/L**	84.4 (79.9-88.3)	70.8 (64.8-76.2)	36.2 (31.6-40.8)	27.0 (23.1-30.9)
			≥7 ng/L	86.4 (82.0-90.1)	73.6 (67.4-78.9)	34.8 (30.1-39.4)	27.0 (23.1-30.9)
			≥8 ng/L	87.1 (82.8-90.7)	74.3 (68.1-79.7)	34.2 (29.6-38.6)	27.0 (23.1-30.9)
			≥9 ng/L	87.4 (83.1-90.9)	74.5 (68.2-79.9)	33.5 (29.0-38.1)	27.0 (23.1-30.9)
			≥10 ng/L	87.4 (83.1-90.9)	74.2 (67.8-79.7)	33.0 (28.5-37.7)	27.0 (23.1-30.9)
	≥80 ng/L	OR	≥6 ng/L	85.4 (80.9-89.2)	71.6 (65.4-77.1)	34.8 (30.3-39.5)	22.0 (18.5-26.0)
			≥7 ng/L	87.4 (83.1-90.9)	74.5 (68.2-79.9)	33.5 (28.9-38.1)	22.0 (18.5-26.0)
			≥8 ng/L	88.1 (83.9-91.5)	75.3 (68.9-80.8)	32.8 (28.3-37.3)	22.0 (18.5-26.0)
			≥9 ng/L	88.4 (84.3-91.8)	75.5 (69.0-81.0)	32.1 (27.6-36.8)	22.0 (18.5-26.0)
			≥10 ng/L	88.4 (84.3-91.8)	75.2 (68.6-80.8)	31.7 (27.1-36.1)	22.0 (18.5-26.0)
	≥100 ng/L	OR	≥6 ng/L	86.1 (81.7-89.8)	72.4 (66.1-77.9)	34.2 (29.5-38.7)	20.0 (16.5-23.9)
			≥7 ng/L	88.1 (83.9-91.5)	75.3 (68.9-80.8)	32.8 (28.3-37.2)	20.0 (16.5-23.9)
			≥8 ng/L	89.1 (85.0-92.4)	76.8 (70.3-82.2)	31.9 (27.4-36.5)	20.0 (16.5-23.9)
			≥9 ng/L	89.4 (85.4-92.6)	77.0 (70.4-82.5)	31.2 (26.8-35.7)	20.0 (16.5-23.9)
			≥10 ng/L	89.4 (65.4-80.5)	76.6 (70.0-82.2)	30.8 (26.4-35.2)	20.0 (16.5-23.9)
	≥160 ng/L	OR	≥6 ng/L	86.4 (82.0-90.1)	72.5 (66.1-78.0)	33.5 (28.8-38.0)	14.4 (11.3-17.8)
			≥7 ng/L	88.7 (84.6-92.1)	75.9 (69.3-81.4)	31.7 (27.2-36.3)	14.4 (11.3-17.8)
			≥8 ng/L	89.7 (85.8-92.9)	77.4 (70.7-82.9)	30.8 (26.3-35.3)	14.4 (11.3-17.8)
			≥9 ng/L	90.1 (86.1-93.2)	77.6 (70.9-83.2)	30.1 (25.8-34.5)	14.4 (11.3-17.8)
			≥10 ng/L	90.1 (86.1-93.2)	77.3 (70.5-82.9)	29.7 (25.3-34.0)	14.4 (11.3-17.8)
	≥320 ng/L	OR	≥6 ng/L	86.8 (82.4-90.4)	73.0 (66.6-78.5)	33.0 (28.8-37.9)	10.6 (7.8-13.6)
			≥7 ng/L	89.4 (85.4-92.6)	77.0 (70.4-82.5)	31.2 (26.7-35.7)	10.6 (7.8-13.6)
			≥8 ng/L	90.4 (86.5-93.5)	78.4 (71.6-83.8)	30.1 (25.8-34.5)	10.6 (7.8-13.6)
			≥9 ng/L	90.7 (86.9-93.8)	78.5 (71.6-84.0)	29.2 (24.8-33.6)	10.6 (7.8-13.6)
			≥10 ng/L	90.7 (86.9-93.8)	78.1 (71.2-83.8)	28.8 (24.3-33.3)	10.6 (7.8-13.6)

n.a. = not applicable. Bold printed cutoff criteria indicate the official ESC cutoff criteria combination for rule-out and rule-in; italic printed cutoff criteria indicate the alternative, modified cutoff criteria combination for patients with renal dysfunction.

Supplemental Table 15: Performance of the official European Society of Cardiology and a modified 0/1h-algorithm in patients with renal dysfunction

Using high-sensitivity cardiac troponin T – n=487

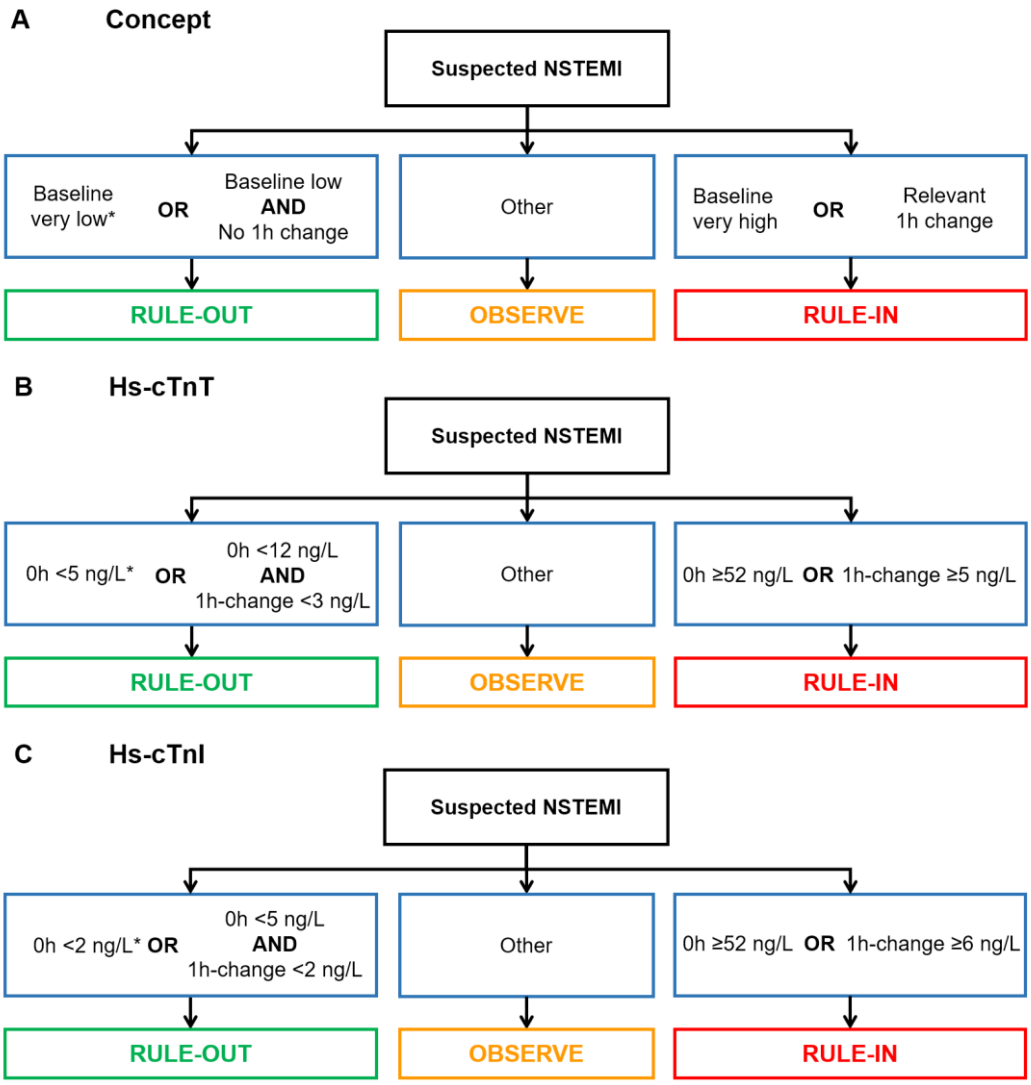
	Official ESC 0/1h-algorithm	Modified 0/1h-algorithm	Change	p-value*
Sensitivity of rule-out	100.0 (97.6-100.0)	100.0 (97.6-100.0)	±0%	1.0
NPV of rule-out	100.0 (n.a.)	100.0 (n.a.)	±0%	1.0
Specificity of rule-in	88.7 (84.8-91.9)	92.6 (89.2-95.1)	+3.9%	**<0.001**
PPV of rule-in	76.5 (70.6-81.6)	81.5 (74.9-86.7)	+5.0%	**0.001**
Proportion ruled-out	18.1 (14.6-21.6)	22.6 (18.8-26.7)	+4.5%	**<0.001**
- based on 0h-sample only	1.4 (0.4-2.6)	1.6 (0.6-2.9)	+0.2%	1.0
- based on 0h/1h-samples	16.6 (13.5-20.0)	21.0 (17.2-24.5)	+4.4%	**<0.001**
Proportion ruled-in	33.3 (29.3-37.5)	27.7 (23.7-31.7)	-5.6%	**<0.001**
- based on 0h-sample	25.9 (22.4-29.7)	15.2 (11.9-18.4)	-10.7%	**<0.001**
- based on 1h-sample	7.4 (5.2-9.6)	12.5 (9.7-15.6)	+5.1%	**0.008**
Overall Efficacy	51.3 (46.8-55.8)	50.3 (45.9-55.2)	-1.0%	0.568
Prevalence of NSTEMI in the observational group	11 (7-15)	17 (12-22)	+6%	**0.010**

Using high-sensitivity cardiac troponin I – n=445

	Official ESC 0/1h-algorithm	Modified 0/1h-algorithm	Change	p-value*
Sensitivity of rule-out	98.6 (95.0-99.8)	98.6 (95.0-99.8)	±0%	1.0
NPV of rule-out	97.4 (90.5-99.4)	98.0 (92.4-99.5)	+0.6%	0.177
Specificity of rule-in	84.4 (79.9-88.3)	88.1 (83.9-91.5)	+3.7%	**0.001**
PPV of rule-in	70.8 (64.8-76.2)	75.3 (68.9-80.8)	+4.5%	**0.004**
Proportion ruled-out	17.5 (13.9-21.4)	22.2 (18.3-26.2)	+4.7%	**<0.001**
- based on 0h-sample only	1.3 (0.4-2.5)	7.6 (5.3-10.2)	+6.3%	**<0.001**
- based on 0h/1h-samples	16.2 (12.7-19.7)	14.6 (11.4-18.2)	-1.6%	0.371
Proportion ruled-in	36.2 (31.6-40.8)	32.8 (28.3-37.2)	-3.4%	**<0.001**
- based on 0h-sample	27.0 (23.1-30.9)	20.0 (16.5-23.9)	-7.0%	**<0.001**
- based on 1h-sample	9.2 (6.5-12.0)	12.8 (9.7-16.1)	+3.6%	**0.004**
Overall Efficacy	53.5 (49.2-58.0)	54.6 (49.8-59.1)	+1.1%	0.500
Prevalence of NSTEMI in the observational group	13 (9-18)	15 (11-20)	+2%	0.390

*Numbers represent percentage (95% confidence interval). * performances measures of the official and the modified 0/1h-algorithms were compared using McNemar test or the method described by Moskowitz et al.[16] Bold printed p-values indicate statistical significance. n.a. = not applicable; NPV = negative predictive value; NSTEMI = Non-ST-Segment-Elevation Myocardial Infarction, PPV = positive predictive value.*

Supplemental Figures

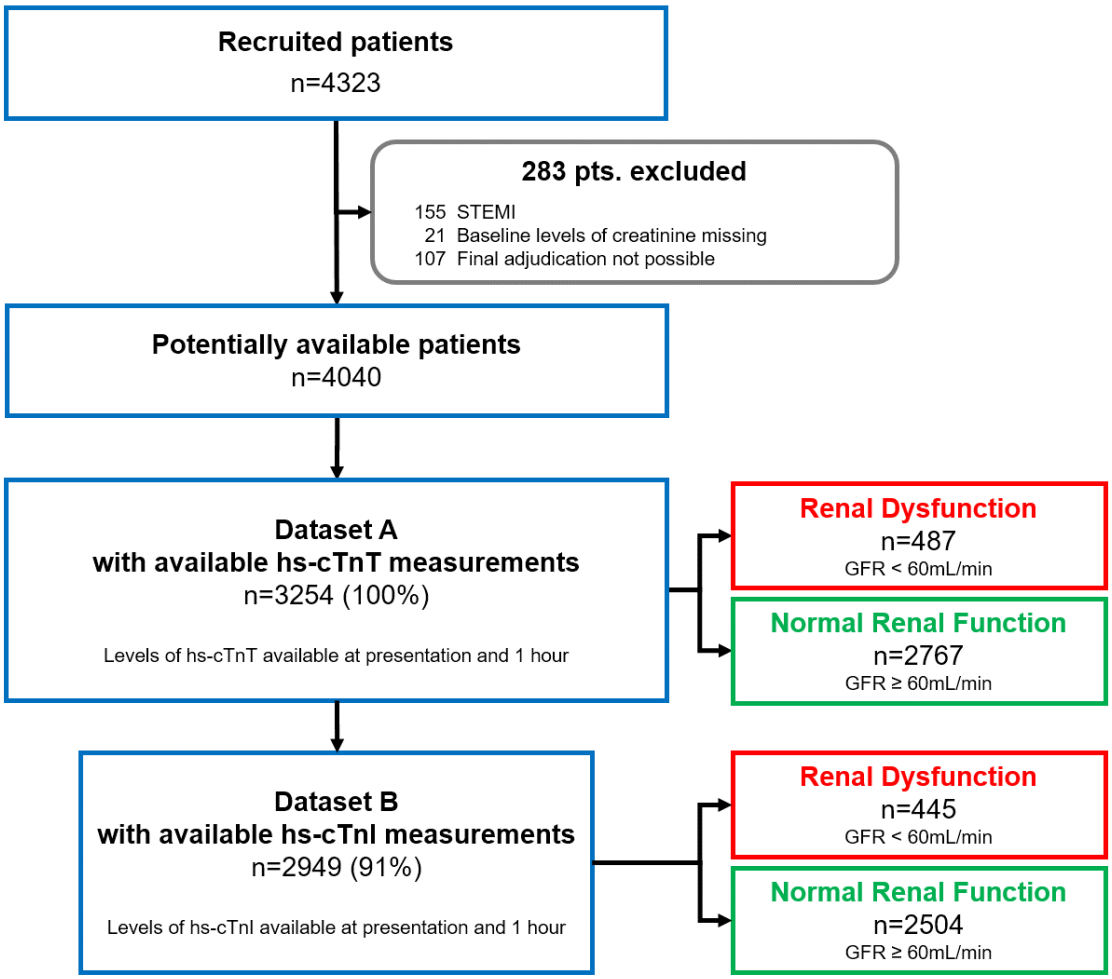


Supplemental Figure 1	**0/1h-algorithm of the European Society of Cardiology to rapidly rule-out and rule-in Non-ST-Segment-Elevation Myocardial Infarction**

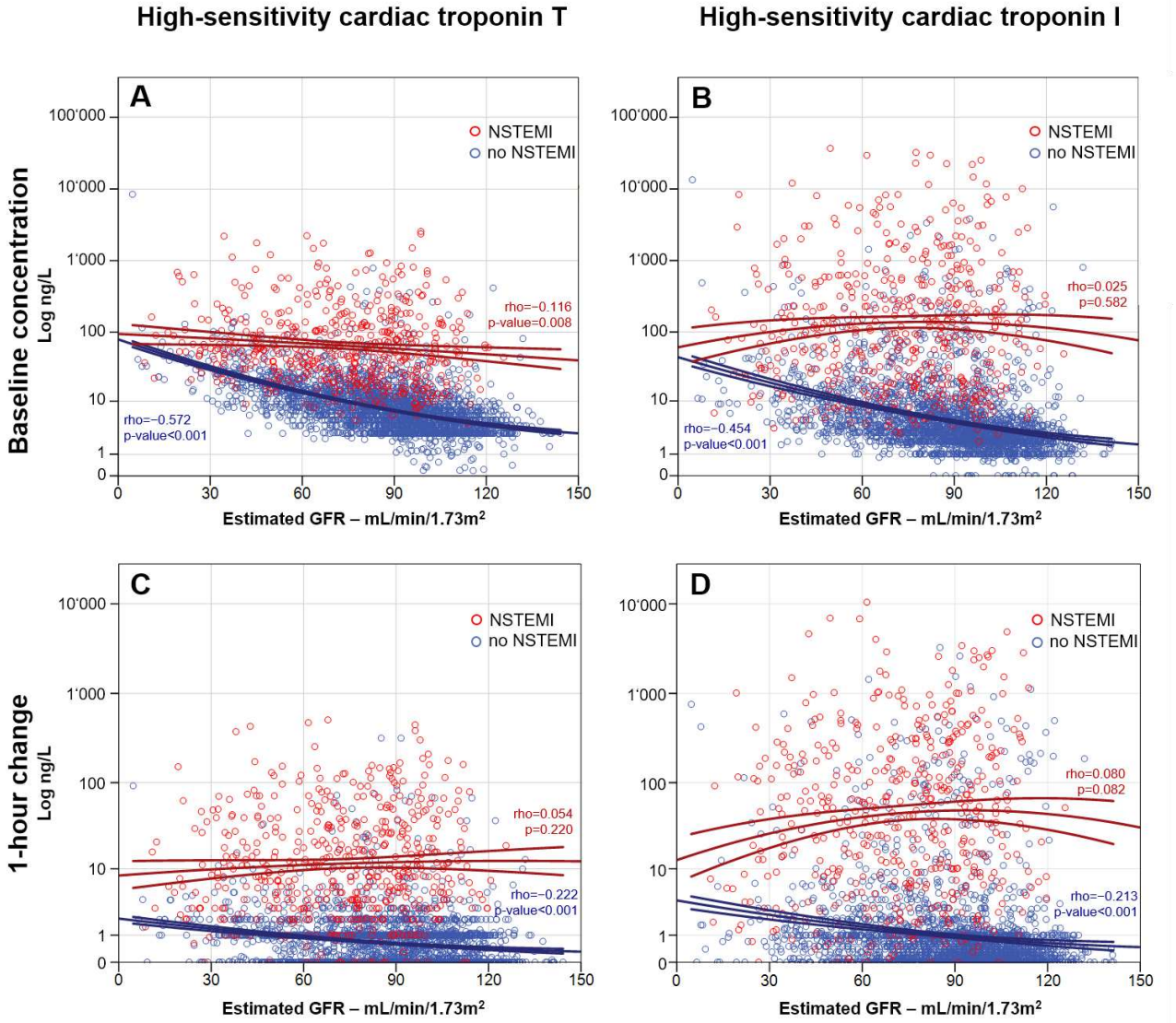
(A) general concept of the European Society of Cardiology 0/1h-algorithm

(B) assay-specific cutoff values for Elecsys high-sensitivity cardiac troponin T

(C) assay-specific cutoff values for Architect high-sensitivity cardiac troponin I



Supplemental Figure 2 **Patient flow diagramm**

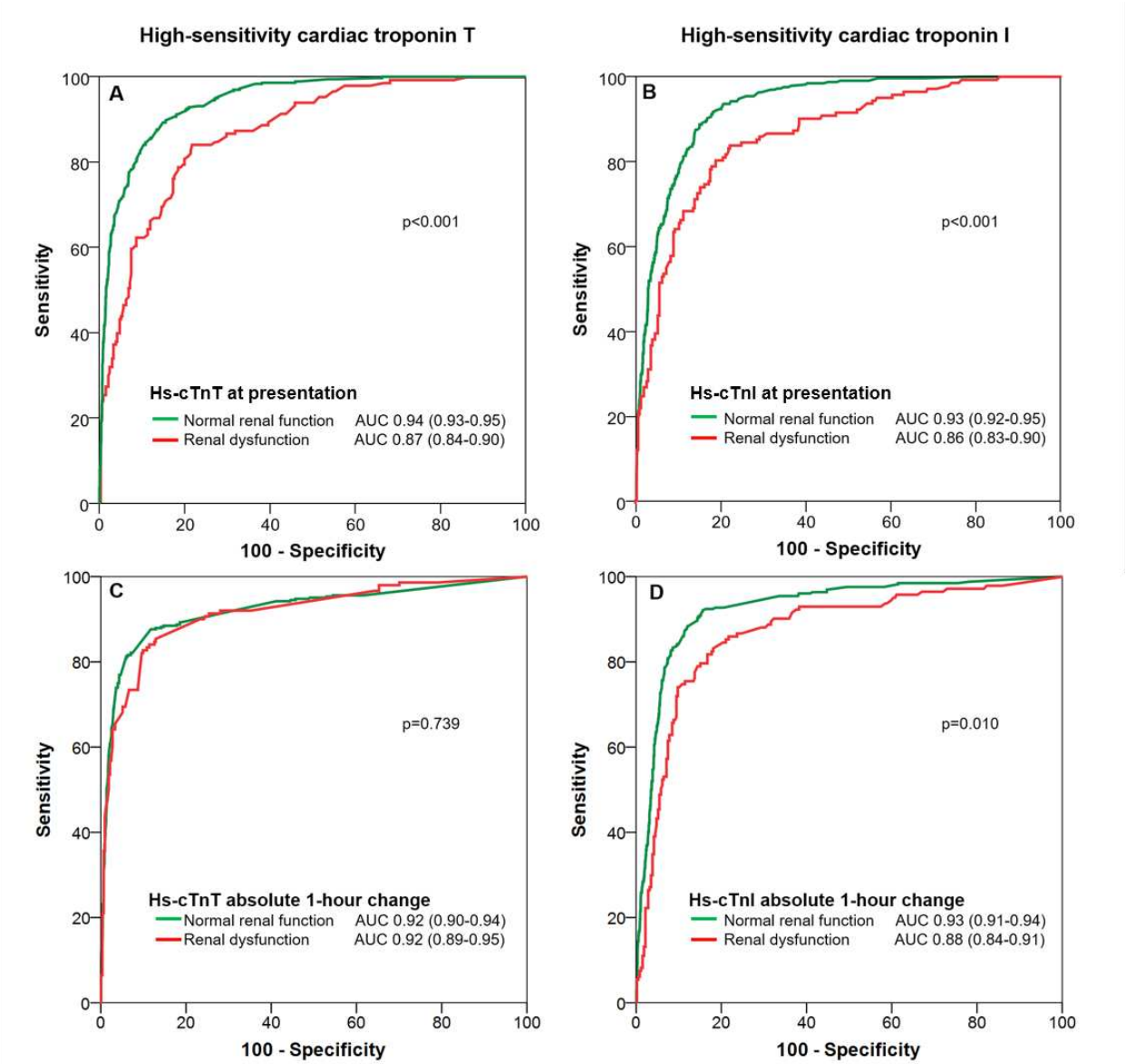


Supplemental Figure 3 **Correlations between glomerular filtration rate and concentrations at presentation and absolute 1-hour changes in high-sensitivity cardiac troponin**

Correlations between renal function expressed by the estimated glomerular filtration rate and:

(A) concentrations of high-sensitivity cardiac troponin T at presentation.
(B) concentrations of high-sensitivity cardiac troponin I at presentation.
(C) absolute 1-hour changes of high-sensitivity cardiac troponin T.
(D) absolute 1-hour changes of high-sensitivity cardiac troponin I.

among patients with acute myocardial infarction (red dots) and without acute myocardial infarction (blue dots). NSTEMI = Non-ST-Segment-Elevation Myocardial Infarction; GFR = glomerular filtration rate.

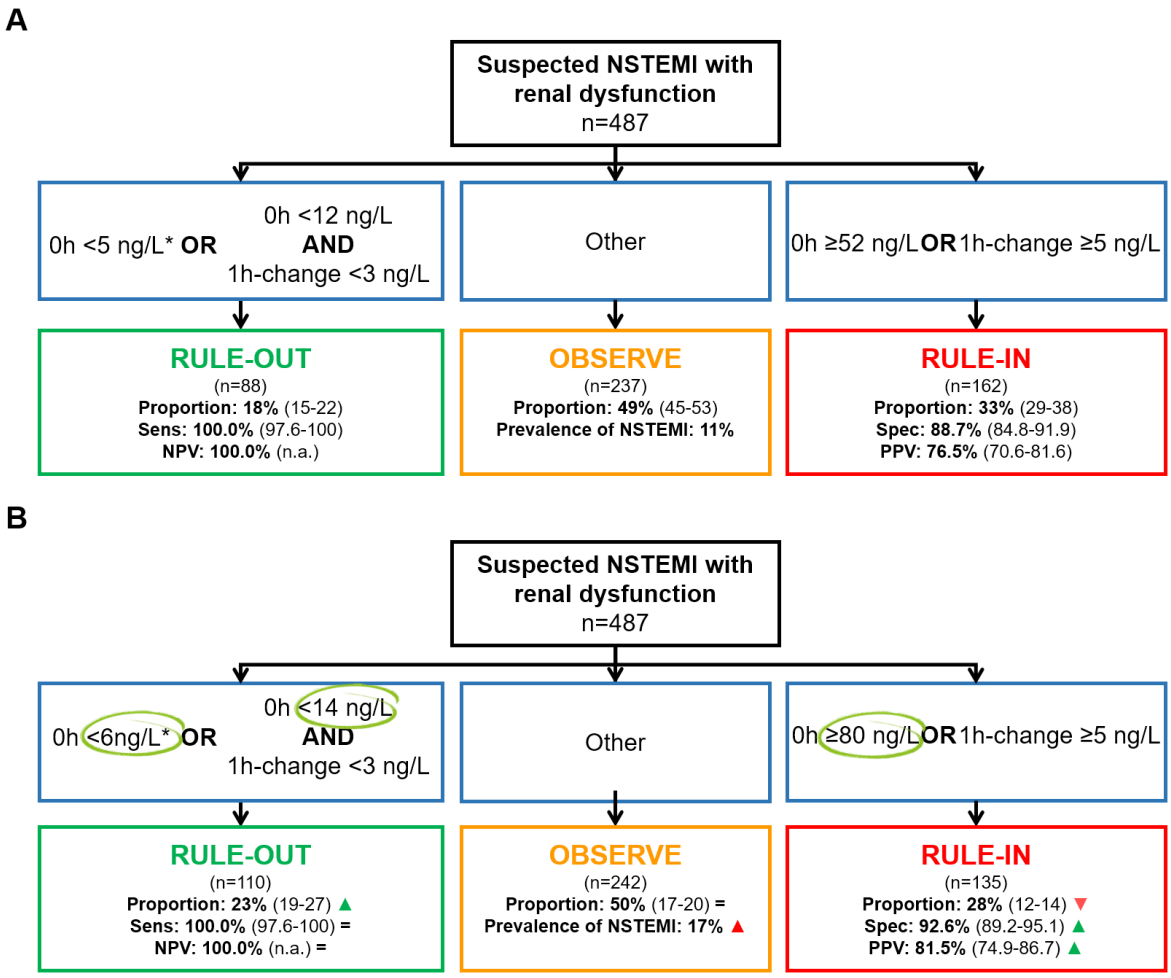


Supplemental Figure 4 **Diagnostic performance of high-sensitivity cardiac troponin in patients with renal dysfunction and normal renal function.**

Receiver-operating characteristic (ROC) curves describing the discriminative performance to identify Non-ST-Segment-Elevation Myocardial Infarction in patients with normal renal function (green line) and renal dysfunction (red line) using:

(A) concentrations of high-sensitivity cardiac troponin T at presentation.
(B) concentrations of high-sensitivity cardiac troponin I at presentation.
(C) absolute 1-hour changes of high-sensitivity cardiac troponin T.
(D) absolute 1-hour changes of high-sensitivity cardiac troponin I.

AUC = Area under the receiver operating characteristic curve with its corresponding 95% confidence interval. P-value for comparison of independent AUC-curves.

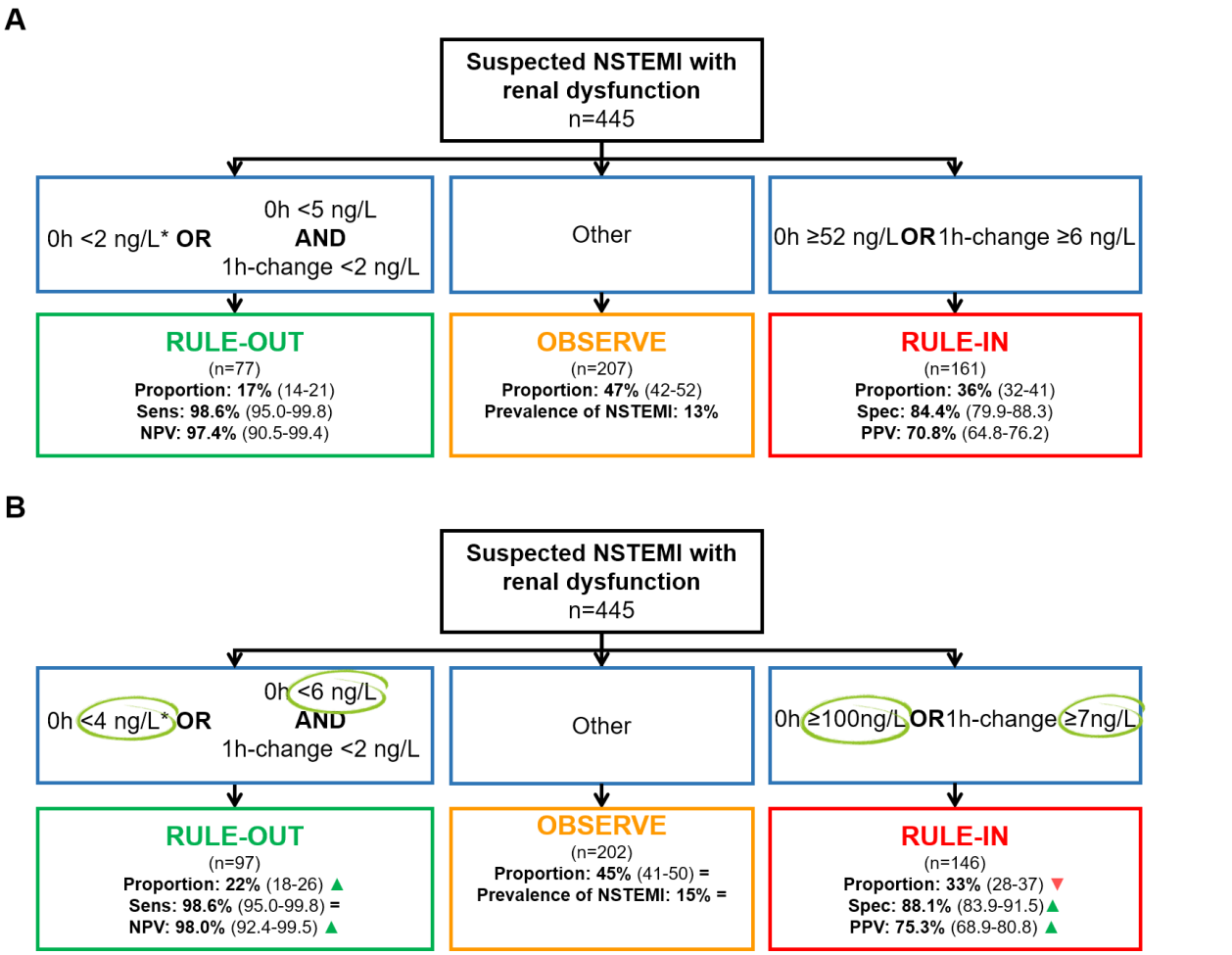


Supplemental Figure 5 **Performance of the official ESC and an alternative, modified 0/1h-algorithm using high-sensitivity cardiac troponin T in patients with renal dysfunction.**

Flow-charts depicting the diagnostic performance of

(A) the official European Society of Cardiology 0/1h-algorithm and
(B) an alternative, modified 0/1h-algorithm

for rule-out and rule-in Non-ST-Segment-Elevation Myocardial Infarction among patients presenting with suspected myocardial infarction and with renal dysfunction using high-sensitivity cardiac troponin T (hs-cTnT, Elecsys). NSTEMI = non-ST-segment elevation myocardial infarction; 1h-change= absolute (unsigned) change of high-sensitivity cardiac troponin T within 1 hour; NPV = negative predictive value; PPV = positive predictive value; n.a. = not applicable. *if chest pain onset > 3 hours before presentation to the emergency department. Green colored curls highlight modified cutoff criteria compared to the official ESC 0/1h-algorithm; ▲ indicates a significant increase of the respective diagnostic parameter using the modified 0/1h-algorithm as compared to the official ESC 0/1h-algorithm, ▼ indicates a significant decrease of the respective diagnostic parameter using the modified 0/1h-algorithm as compared to the official ESC 0/1h-algorithm, = indicates no significant change between the two algorithms. Green colored arrows indicate favorable change, red colored arrows indicate unfavorable change using the modified 0/1h-algorithm as compared to the original 0/1h-algorithm.

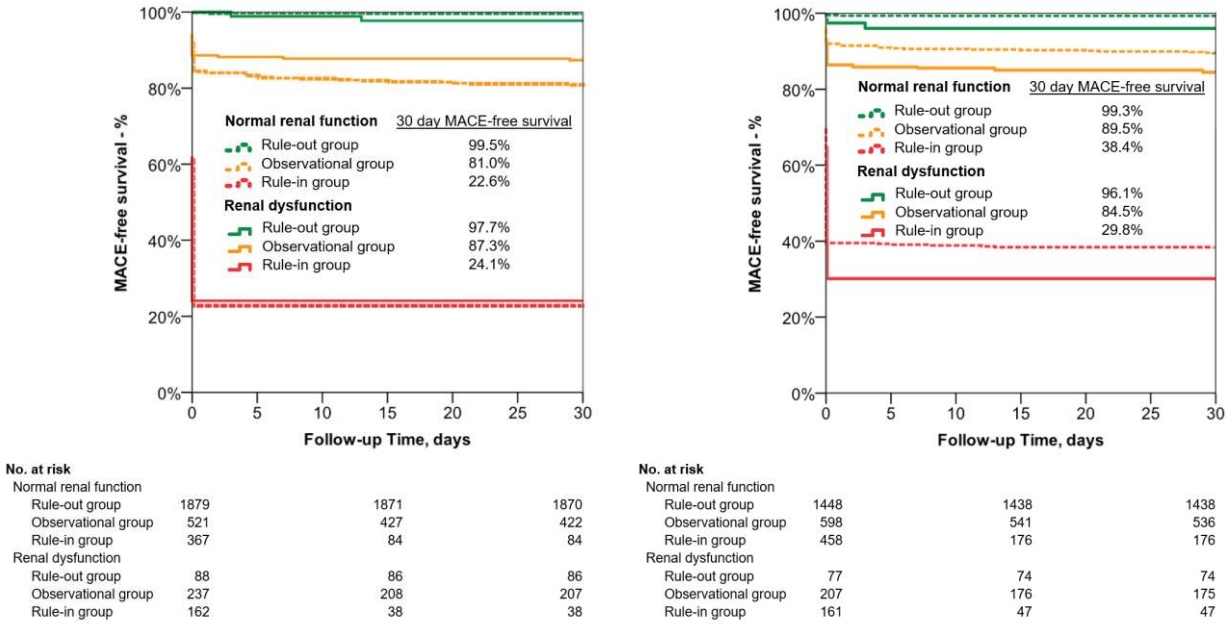


Supplemental Figure 6 **Performance of the official ESC and an alternative, modified 0/1h-algorithm using high-sensitivity cardiac troponin I in patients with renal dysfunction.**

Flow-charts depicting the diagnostic performance of

(A) the official European Society of Cardiology 0/1h-algorithm and
(B) an alternative, modified 0/1h-algorithm

for rule-out and rule-in Non-ST-Segment-Elevation Myocardial Infarction among patients presenting with suspected myocardial infarction and with renal dysfunction using high-sensitivity cardiac troponin I (hs-cTnI, Architect). NSTEMI = non-ST-segment elevation myocardial infarction; 1h-change= absolute (unsigned) change of high-sensitivity cardiac troponin I within 1 hour; NPV = negative predictive value; PPV = positive predictive value; n.a. = not applicable. *if chest pain onset > 3 hours before presentation to the emergency department. Green colored curls highlight modified cutoff criteria compared to the official ESC 0/1h-algorithm; ▲ indicates a significant increase of the respective diagnostic parameter using the modified 0/1h-algorithm as compared to the official ESC 0/1h-algorithm, ▼ indicates a significant decrease of the respective diagnostic parameter using the modified 0/1h-algorithm as compared to the official ESC 0/1h-algorithm, **=** indicates no significant change between the two algorithms. Green colored arrows indicate favorable change, red colored arrows indicate unfavorable change using the modified 0/1h-algorithm as compared to the original 0/1h-algorithm.



Supplemental Figure 7 **MACE-free survival according to risk stratification group by the European Society of Cardiology 0/1h-algorithm using high-sensitivity cardiac troponin T and I in patients with normal renal function and renal dysfunction.**

Kaplan-Meier curves depicting major adverse cardiac events (MACE)-free survival within 30 days for patients with normal renal function (dashed lines) and renal dysfunction (full lines) stratified by the European Society of Cardiology 0/1h-algorithm to the rule-out (green lines), observational (orange lines) and rule-in (red lines) group

(A) using high-sensitivity cardiac troponin T (left panel)

(B) using high-sensitivity cardiac troponin I (right panel).

MACE = major adverse cardiac events, defined as the composite of all-cause mortality, myocardial infarction (including index event), cardiogenic shock, ventricular tachyarrhythmias, or higher-degree atrioventricular block.

Supplemental References

1. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernandez-Aviles F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D and Al-Attar N. Universal definition of myocardial infarction. *Circulation*. 2007;116:2634-2653.

2. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol C, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C and Luis Zamorano J. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267-315.

3. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ, Members AATF, Society for Cardiovascular A, Interventions and the Society of Thoracic S. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2354-2394.

4. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, Huber K, Plebani M, Biasucci LM, Tubaro M, Collinson P, Venge P, Hasin Y, Galvani M, Koenig W, Hamm C, Alpert JS, Katus H and Jaffe AS. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J*. 2012;33:2252-2257.

5. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ and Mendis S. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020-2035.

6. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, Meissner J, Haaf P, Potocki M, Drexler B, Osswald S and Mueller C. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation*. 2011;124:136-145.

7. Irfan A, Reichlin T, Twerenbold R, Meister M, Moehring B, Wildi K, Bassetti S, Zellweger C, Gimenez MR, Hoeller R, Murray K, Sou SM, Mueller M, Mosimann T, Reiter M, Haaf P, Ziller R, Freidank H, Osswald S and Mueller C. Early diagnosis of myocardial infarction using absolute and relative changes in cardiac troponin concentrations. *Am J Med*. 2013;126:781-788 e2.

8. Wildi K, Reichlin T, Twerenbold R, Mader F, Zellweger C, Moehring B, Stallone F, Minners J, Rubini Gimenez M, Hoeller R, Murray K, Sou SM, Mueller M, Denhaerynck K, Mosimann T, Reiter M, Haaf P, Meller B, Freidank H, Osswald S and Mueller C. Serial changes in high-sensitivity cardiac troponin I in the early diagnosis of acute myocardial infarction. *Int J Cardiol*. 2013;168:4103-4110.

9. Biener M, Mueller M, Vafaie M, Keller T, Blankenberg S, White HD, Katus HA and Giannitsis E. Comparison of a 3-hour versus a 6-hour sampling-protocol using high-sensitivity cardiac troponin T for rule-out and rule-in of non-STEMI in an unselected emergency department population. *Int J Cardiol*. 2013;167:1134-1140.

10. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, Katus HA and Giannitsis E. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. *Clin Chem*. 2012;58:209-218.

11. Biener M, Giannitsis E, Lamerz J, Mueller-Hennessen M, Vafaie M and Katus HA. Prognostic value of elevated high-sensitivity cardiac troponin T levels in a low risk outpatient population with cardiovascular disease. *European heart journal Acute cardiovascular care*. 2016;5:409-418.

12. Wu AH, Lu QA, Todd J, Moecks J and Wians F. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. *Clin Chem*. 2009;55:52-58.

13. Nordenskjold AM, Ahlstrom H, Eggers KM, Frobert O, Jaffe AS, Venge P and Lindahl B. Short- and long-term individual variation in cardiac troponin in patients with stable coronary artery disease. *Clin Chem*. 2013;59:401-409.

14. Aakre KM, Roraas T, Petersen PH, Svarstad E, Sellevoll H, Skadberg O, Saele K and Sandberg S. Weekly and 90-minute biological variations in cardiac troponin T and cardiac troponin I in hemodialysis patients and healthy controls. *Clin Chem*. 2014;60:838-847.

15. Hammarsten O, Fu ML, Sigurjonsdottir R, Petzold M, Said L, Landin-Wilhelmsen K, Widgren B, Larsson M and Johanson P. Troponin T percentiles from a random population sample, emergency room patients and patients with myocardial infarction. *Clin Chem*. 2012;58:628-637.

16. Moskowitz CS and Pepe MS. Comparing the predictive values of diagnostic tests: sample size and analysis for paired study designs. *Clin Trials*. 2006;3:272-279.